IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor	:	Breitenbach et al.
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Filing Date	:	April 26, 2005
For:	:	HIGHLY PURE BASES OF 3,3-DIPHENYL PROPYLAMINE MONOESTERS
Examiner	:	Valenrod
Art Unit	:	1621

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Date: January 13, 2010
Signature: /Daniel G. Harris/
Daniel G. Harris

APPEAL BRIEF

Sir:

Appellants filed a Notice of Appeal on September 15, 2009. Appellants hereby request a two-month extension of time for filing the Appeal Brief. The $490 extension of time fee and the $540 Appeal Brief fee are being paid by credit card. The Director is hereby authorized to charge Kenyon & Kenyon LLP's **Deposit Account No. 11-0600** for any additional fee(s) or underpayments of fee(s) under 37 C.F.R. 1.16 and 1.17, and to credit any overpayments.

Real Party in Interest

The real parties in interest for the present application are:

Schwarz Pharma AG
Alfred-Nobel-Str. 10 - 40789 Monheim
Germany

Schwarz Pharma AG is wholly owned by:

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Brussels
Belgium

The present application is exclusively licensed to:

Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Related Appeals and Interferences

There are no related appeals and interferences.

Status of claims

Claims 35-39 and 70-72 are pending, are under rejection, and are being appealed. Claims 1-34 and 40-69 have been canceled.

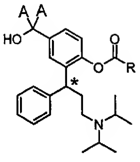
Status of Amendments

An Amendment After Final was filed on September 14, 2009. No claims were amended in the Amendment After Final. An Advisory Action was issued on October 13, 2009. The Advisory Action did not explicitly state that the Amendment After Final was entered but did state that the rejection under 35 U.S.C. §103(a) had been overcome by the Amendment After Final.

Summary of Claimed Subject Matter

The following is a summary of the subject matter of the independent claim being appealed.

The invention defined by independent claim 35 is a compound having the structure of Formula I:



Formula I

wherein each A is independently hydrogen or deuterium, R is C_{1-6}-alkyl, C_{3-10}-cycloalkyl or phenyl, which may each be substituted with C_{1-3}-alkoxy, fluorine, chlorine, bromine, iodine, nitro, amino, hydroxyl, oxo, mercapto or deuterium and where the C-atom marked with a star "*" may be present in the (R)-configuration, the (S)-configuration or as a mixture of such configurations **{specification, page 4, lines 11-19}** where the compound is present as a free base **{specification, page 4, line 4}** with a salt content of less than 10% by weight **{specification, page 20, lines 16-17}** and in a degree of purity of above 97 percent by weight **{specification, page 4, lines 4-5; page 4, lines 21-22}** and wherein the free base is present in an amount sufficient for a dosing unit **{specification, page 16, lines 16-23}**.

Grounds of Rejection to be Reviewed on Appeal

The following grounds of rejection are present in this appeal:

(1) Are claims 35-39 and 70-72 indefinite under 35 U.S.C. §112, second paragraph?

(2) Are claims 35-39 and 70-72 anticipated under 35 U.S.C. §102(b) by International Patent Publication WO 99/58478?

Argument

Ground of rejection 1

Are claims 35-39 and 70-72 indefinite under 35 U.S.C. §112, second paragraph?

According to the Office Action issued June 15, 2009, the recitation of the words "dosing unit" in claim 35 makes it unclear whether claim 35 and the claims dependent therefrom are directed to a compound or to a pharmaceutical formulation or composition. See the Office Action issued June 15, 2009, paragraph bridging pages 2 and 3:

> The rejected claims are directed to a compound of formula (I), however the newly amended claims now comprise limitations directed to a "dosing unit" which is described as a pharmaceutical formulation (page 16, lines 20-21 of the specification). It is not clear if the applicant is claiming a compound or a composition.

The Appellants respectfully submit that the Examiner has misunderstood how the term "dosing unit" is being used in claim 35. The presence of the term "dosing unit" in claim 35 does not transform claim 35 from a compound claim to a formulation or composition claim. Instead, "dosing unit" is merely being used in claim 35 to indicate the <u>amount</u> of the recited compound that is within the scope of claim 35.

The grammatical structure of claim 35 bears this out. The term "dosing unit" appears in the phrase "sufficient for a dosing unit." This phrase immediately follows the word "amount" and thus refers back to the word "amount" by specifying a particular value for "amount." Consistent with the grammatical structure of this claim, the phrase "sufficient for a dosing unit" could be replaced by a phrase that specifies a different amount, e.g., "of at least 3 mg." If that

were done, the entire limitation at issue would read "wherein the free base is present in an amount of at least 3 mg." It should be clear that such language would not cause any doubt about whether claim 35 refers to a compound rather than a formulation or composition. Similarly, the actual language of claim 35 ("wherein the free base is present in an amount sufficient for a dosing unit") should not cause any such doubt.

When assessing indefiniteness, the general rules of claim construction apply. *See, e.g., Young v. Lumenis Inc.*, 492 F. 3d 1336, 1346, 83 U.S.P.Q. 2d 1191, 1197 (Fed. Cir. 2007): "[W]e have explained that 'in the face of an allegation of indefiniteness, general principles of claim construction apply.'" [quoting *Datamize, LLC v. Plumtree Software, Inc.,* 417 F. 3d 1342, 75 U.S.P.Q. 2d 1801 (Fed. Cir. 2005)]

One of the general rules of claim construction applicable to this rejection for indefiniteness is that disputed terms of a claim are to be read in context, not as single elements in isolation. *See, e.g., Hockerson-Halberstadt, Inc. v. Converse, Inc.*, 183 F. 3d 1369, 1374, 51 U.S.P.Q. 2d 1518, 1522 (Fed. Cir. 1999): "Proper claim construction, however, demands interpretation of the entire claim in context, not a single element in isolation."

With these rules of claim interpretation in mind, the above discussion makes it clear that "dosing unit" should not be interpreted by plucking it out of the context of the phrase "amount sufficient for a dosing unit" and interpreting it on its own. It must be understood as part of that phrase, and that phrase must be understood as specifying an amount for the claimed compound, not as changing the overall claim from a compound claim to a pharmaceutical formulation or a pharmaceutical composition claim.

This is especially clear when one considers that claim 35 does not mention pharmaceutically acceptable carriers or excipients, which are typically recited in pharmaceutical formulation or pharmaceutical composition claims.

In view of the grammatical features of claim 35 discussed above, and the lack of any mention of pharmaceutically acceptable carriers or excipients, one of ordinary skill in the art would not reasonably interpret claim 35 as being directed to a pharmaceutical formulation or a pharmaceutical composition.

In the Advisory Action issued October 13, 2009, the Examiner argued (for the first time) that the purity recitation of claim 35 also makes claim 35 indefinite. See the Advisory Action issued October 13, 2009, page 2:

> Since the claims are directed to a compound NOT to a composition it is unclear how a compound can be 97% pure. A compound is inherently pure. If its [sic] 97% pure as applicants claim, then there are 3% of other materials present. A compound plus the 3% of other materials make a composition.

The Examiner is apparently of the opinion that a compound claim may not recite purity limitations without causing indefiniteness. This opinion, however, is inconsistent with *In re Bergstrom,* 427 F. 2d 1394, 166 U.S.P.Q. 256 (C.C.P.A. 1970). In *Bergstrom*, the court was faced with a claim that recited a chemical structure followed by a purity limitation. The court referred to that claim as relating to a chemical <u>compound</u>.

> The invention relates to two chemical <u>compounds</u>, as reflected in the claims:
>
> 23. 7-[3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentyl]-5-heptenoic acid, said acid being sufficiently pure to give a substantially ideal curve on partition

> chromatography using an ethylene chloride:heptane:acetic acid:water (15:15:6:4) solvent system.
>
> 427 F. 2d at 1395, 166 U.S.P.Q. at 256. [underscoring added]

In view of the discussion above, the Appellants submit that the presently appealed claims are not indefinite.

Ground of rejection 2

Are claims 35-39 and 70-72 anticipated under 35 U.S.C. §102(b) by International Patent Publication WO 99/58478 (Meese)?

The claims have been rejected as being anticipated by the disclosure of Meese at page 11, lines 13-14. This disclosure provides the chemical name of a compound. Claim 39 recites the chemical name of the same compound.[1]

Page 11, lines 13-14, of Meese reads, in its entirety:

> R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

Thus, this portion of Meese discloses nothing but a chemical name. In particular, this portion of Meese makes no mention of salt content, degree of purity, or amount. Nevertheless, according to the Office Action issued June 15, 2009, this recitation in Meese of the mere chemical name of the compound is enough to satisfy all the limitations of the appealed claims

1 Although Meese and claim 39 use somewhat differently terminology, the names recited by Meese and claim 39 refer to the same compound.

with respect to purity, salt content, and amount. See the Office Action issued June 15, 2009, page 3:

> Meese et al disclose R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (page 11, lines 13-14), (the compound of the instant claim 39). The above compound is disclosed as a free base of R configuration and is inherently pure. The limitations directed to the dosing unit is inherently met by the compound of Meese et al. because the term "dosing unit" as defined in the instant specification is open to any amount of the active ingredient (page 16, lines 20-25 of the specification).

The presently appealed claims all require a salt content of "less than 10% by weight," a degree of purity of "above 97% by weight," and "an amount [of free base] sufficient for a dosing unit."[2] Meese provides no disclosure of the compound R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester having this salt content, degree of purity, or amount. Meese provides the name of the compound and nothing more.

With respect to the limitation "amount sufficient for a dosing unit," Meese supposedly inherently meets this limitation because "the term 'dosing unit' as defined in the instant specification is open to any amount of the active ingredient (page 16, lines 20-25 of the specification)." See the above quote from the Office Action issued June 15, 2009.

The Appellants respectfully submit that page 16, lines 20-25, of the specification does not support the position that "dosing unit" is open to any amount of the active ingredient. This portion of the specification defines a dosing unit as containing enough active ingredient to

[2] These are the limitations recited in appealed claim 35, from which all the other appealed claims depend. Certain of the dependent appealed claims recite even higher levels of purity.

release a therapeutically effective amount of active ingredient. Page 16, lines 20-25, of the specification reads as follows:

> In this patent application the expression 'dosing unit' is understood to mean a pharmaceutical formulation that contains a defined amount of active ingredient and that releases this following the one-time administration in patients over a predetermined period of time <u>in a therapeutically effective amount</u>. [underscoring added]

Thus an "amount sufficient for a dosing unit" is at least a therapeutically effective amount. A "therapeutically effective amount" is not just "any amount;" it must be enough to provide a therapeutic benefit. Since Meese does not disclose this amount of the compound at issue, to say nothing of the other limitations at issue, Meese cannot anticipate the presently appealed claims.

Even if, for the sake or argument, the disclosure at page 11, lines 13-14, of Meese is viewed as disclosing the salt content, degree of purity, and amount of the free base recited in the presently appealed claims, Meese would not anticipate the presently appealed claims because Meese discloses no method for obtaining the compound at issue having the salt content, degree of purity, and amount recited in the presently appealed claims. Furthermore, when the present inventors tried to obtain the compound at issue having the salt content, degree of purity, and amount recited in the presently appealed claims using the methods of the prior art, they did not succeed.

Meese discloses a general process for making phenolic monoesters such as the compound at issue on page 59, line 22, to page 60, line 12. The process involves reacting a carboxylic acid

monochloride with (±)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol in dichloromethane and then adding triethylamine.

When this process was carried out by the present inventors with isobutyric acid chloride as the carboxylic acid monochloride and R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, the resulting R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (the compound at issue) was found to have a degree of purity of only 94.1% and, typically, this process gave degrees of purity that were even lower (i.e., 90.5%-94.4%). See the present application, page 42, line 27, to page 43, line 8:

> A. <u>Manufacture of the Fesoterodine Base (B, see FIG. 1. R = i-Pr)</u>
> Drops of a solution of 18.6 g isobutyric acid chloride in 250 ml dichloromethane were added in approximately 10 minutes to a solution of 59.8 g (175.1 mol) (R)-2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol cooled to -3°C. (A, see FIG. 1) dissolved in 750 ml dichloromethane with agitation and cooling by ice bath. A white substance precipitated after approximately 5 minutes. For this purpose drops of a solution of 17.7 g triethylamine in 250 ml dichloromethane were added in 5 minutes under agitation and ice bath cooling. The batch was washed once with each of 250 ml water, 250 ml approximate 5% aqueous $NaHCO_3$ solution and 250 ml water. The dichloromethane extract dried over Na_2SO_4 was evaporated to a low small bulk on a rotary evaporator to constant weight, whereby a pale yellow, high viscosity oil was left.
> Raw yield: 63.7 g (88.5% of the theory).
> The purity of B in the HPLC in this example amounted to 94.1%. Typical range for B: 90.5% -94.4%.4 %. Decomposition occurred in the case of the high vacuum distillation trial with the formation of A and C.

See also the present application, at page 2, line 29, to page 3, line 13:

> The bases of 3,3-diphenylpropylamines published in WO 99/58478 [Meese] are manufactured by 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol being converted under alkaline conditions with an appropriate acid chloride, for example, isobutyric acid chloride (see Example Execution 3aa of WO 99/58478).

> This reaction, however, only leads disadvantageously to approximately 90% up to a maximum approximate 94% of the desired main product (B). The product consistently contains 6-10% impurities of the starting substance (A), the used acylation agent as well as undesired reaction products in the form of the corresponding di-ester of the acylating reagent used (C) of the monoester (D) of the 4-hydroxy group (see FIG. 1) as well as by dimerization/polymerization.
>
> Attempts by the inventor of this patent application to make the synthesis reaction more selective by, for example, varying the amount of the acylating reagent and/or the acylating conditions (temperature, solvent, concentrations, sequence of the addition, among other things), did not lead to the desired result.
>
> Even extensive trials to purify the high purity base from the product mix in the amounts required for pharmaceutical purposes using conventional procedures remained unsuccessful.

Thus, the evidence of record indicates that Meese does not enable the production of a compound having the level of salt content and degree of purity recited in the present claims and in sufficient amounts required to satisfy the limitations of the appealed claims with respect to amount. The Examiner has pointed to nothing in the prior art that remedies this defect in Meese.

Since what is being claimed in the present application is not merely a compound having the name disclosed at page 11, lines 13-14, of Meese, but instead is that compound having a specified salt content and degree of purity, in an amount sufficient for a dosing unit, Meese cannot anticipate such a claimed compound unless Meese enables the production of such a compound. Case law holds that a putatively anticipating prior art reference must do more than merely name claimed subject matter; it must enable the claimed invention by placing the public in possession of that subject matter.

See, e.g., *Elan Pharmaceuticals, Inc. v. Mayo Foundation*, 346 F. 3d 1051, 1055, 68 U.S.P.Q. 2d 1373, 1376 (Fed. Cir. 2003): "The disclosure in an assertedly anticipating reference

must be adequate to enable possession of the desired subject matter. It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation."

See also *Ex parte Wall*, 156 U.S.P.Q. 95 (Bd. App. 1964), where the Board considered an examiner's rejection under 35 U.S.C. §102 of a claim reading "Perfluorostyrene." In reversing the examiner, the Board commented that the examiner did not contend that the reference disclosed how perfluorostyrene is made, nor did he point to any extraneous evidence which would indicate that those skilled in the art knew how to make that compound. As a result, the rejection under 35 U.S.C. §102 could not stand. The Board stated, at 156 U.S.P.Q. 96:

> The stated position of the examiner is that the naming of the compound of appealed claim 1 in the Dittman et al. reference, published more than a year prior to the filing of the instant case, is sufficient to defeat the appealed claim.
> ...
> Appellants contend that the description of the compound of the appealed claim in the Dittman et al. patent is not sufficient to satisfy the term "described" as that term is used in 35 U.S.C. 102(b). It is the expressed view of appellants that the mere mention of perfluorostyrene in the patent, without a disclosure of how to make the compound, is not sufficient to put the public in possession of the claimed invention and accordingly the reference cannot defeat the appealed claim.
> ...
> After careful consideration of the facts of the present application in the light of the case law, we are of the opinion that the mere mention of perfluorostyrene in the Dittman patent, without more, is insufficient disclosure to put the public in possession of the invention defined by the appealed claim, and that the invention is accordingly not "described in a printed publication" as that clause of 35 U.S.C. 102(b) is interpreted in the LeGrice decision. We accordingly will not sustain the rejection of appealed claim 1.

The Board in *Wall* quoted approvingly from *Phillips Petroleum Co. v. Ladd*, 219 F. Supp. 366, 370, 138 U.S.P.Q. 421, 424 (D.D.C. 1963): "A mere naked formula for a chemical compound which teaches the art nothing about the product which it may represent, and does not

put anyone in possession of the invention, is not the type of statement that should be relied upon for anticipation."

By failing to teach how to make the presently claimed compound, including its limitations with respect to salt content, purity, and amount, Meese does not place the presently claimed compound in the possession of the public, does not enable the presently claimed invention, and thus cannot support an anticipation rejection.

Conclusion

For the reasons discussed above, the Appellants respectfully request that the Board of Patent Appeals and Interferences reverse:

(1) the rejection of claims 35-39 and 70-72 for indefiniteness under 35 U.S.C. §112, second paragraph; and

(2) the rejection of claims 35-39 and 70-72 for anticipation under 35 U.S.C. §102(b) by International Patent Publication WO 99/58478 (Meese).

Respectfully Submitted,

Date: January 13, 2010

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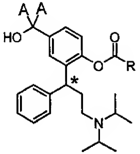
CLAIMS APPENDIX

1-34. (canceled)

35. A compound of the following Formula I:



Formula I

wherein each A is independently hydrogen or deuterium, R is C_{1-6}-alkyl, C_{3-10}-cycloalkyl or phenyl, which may each be substituted with C_{1-3}-alkoxy, fluorine, chlorine, bromine, iodine, nitro, amino, hydroxyl, oxo, mercapto or deuterium and where the C-atom marked with a star "*" may be present in the (R)-configuration, the (S)-configuration or as a mixture of such configurations,

and the compound is present as a free base with a salt content of less than 10% by weight and in a degree of purity of above 97 percent by weight and wherein the free base is present in an amount sufficient for a dosing unit.

36. A compound of claim 35 wherein R is selected from the group consisting of methyl, ethyl, isopropyl 1,1-propyl, 1-butyl, 2-butyl, tertiary-butyl, iso-butyl, pentyl and hexyl.

37. A compound of claim 35 wherein the compound is 2-[3-(1,1-diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate.

38. A compound of claim 35 wherein the C-atom marked with "*" is present in the (R)-configuration.

39. A compound of claim 35 wherein the compound is (R)-2-[3-(1,1-diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate (Fesoterodine).

40-69. (canceled)

70. A compound of claim 35 wherein the degree of purity is above 98 percent by weight.

71. A compound of claim 35 wherein the degree of purity is above 98.5 percent by weight.

72. A compound of claim 35 wherein the degree of purity is above 99 percent by weight.

EVIDENCE APPENDIX

The evidence relied upon, and where in the record that evidence was entered, is as follows:

(1) International Patent Publication WO 99/58478 (Meese). Meese was applied by the Examiner in an anticipation rejection in the Office Action dated November 21, 2006 (see page 3). Meese was also listed in the Information Disclosure Statement filed April 26, 2005.

RELATED PROCEEDING APPENDIX

(none)

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A1

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Published
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(54) Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

(57) Abstract

The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

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Description

Novel derivatives of 3,3-diphenylpropylamines

The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions, but also the main part of the contractions in the overactive bladder resulting in symptoms such as urinary frequency, urgency and urge incontinence. For this reason, antimuscarinic drugs have been proposed for the treatment of bladder overactivity.

Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder overactivity. The effectiveness of oxybutynin has been demonstrated in several clinical studies, but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the most common experienced side effect which may be severe enough to

result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

Tolterodine is a new, potent and competitive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al., 1997, Tolterodine - a new bladder-selective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195-207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite are almost identical to those of tolterodine (Nilvebrant et al., 1997, Eur. J. Pharmacol. 327 (1997), 195-207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite gives a major contribution to the clinical effect in most patients.

WO 94/11337 proposes the active metabolite of tolterodine as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage com-

pared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

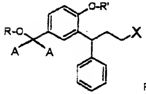
However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability, leading to pre-systemic side effects or interactions due to non-absorbed antimuscarinic drug. In a method to circumvent this disadvantage, different prodrugs of the metabolite have been synthesized and tested for their antimuscarinic activity, potential absorption through biological membranes and enzymatic cleavage.

It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is a further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption through biological membranes of the drugs or an unfavourable metabolism.

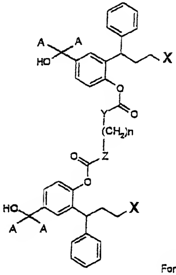
A further object of the invention is to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds

and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

According to the present invention, novel 3,3-diphenylpropyl-amines are provided, which are represented by the general formulae I and VII'



Formula I



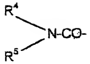
Formula VII'

wherein R and R' are independently selected from

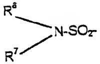
a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryl-oxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d) 

wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

e) 

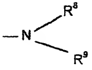
wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unstubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

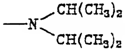
The aforementioned compounds can form salts with physiologically acceptable organic and inorganic acids. Furthermore, the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide and the like.

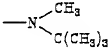
When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

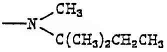
Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

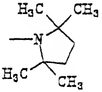
According to another embodiment of the invention, at least one of R^8 and R^9 comprises a branched carbon chain.

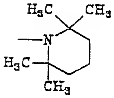
Presently preferred tertiary amino groups X in formula I include the following groups a) to h):

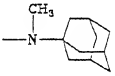
a) 

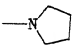
b) 

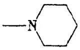
c) 

d) 

e) 

f) 

g) 

h) 

Group a) is particularly preferred.

The aforementioned tertiary amino groups X are described in WO 94/11337 and the compounds according to the present invention can be obtained by using the corresponding starting compounds.

In the compounds according to the present invention, the term "alkyl" preferably represents a straight-chain or branched-chain hydrocarbon group having 1 to 6 carbon atoms. Such hydrocarbon groups may be selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The term "cycloalkyl" denotes a cyclic hydrocarbon group having 3 to 10 carbon atoms which may be substituted conveniently.

The term "substituted or unsubstituted benzyl" denotes a benzyl group $-CH_2-C_6H_5$ which is optionally substituted by one or more substituents on the phenyl ring. Suitable substituents are selected from alkyl, alkoxy, halogen, nitro and the like. Suitable halogen atoms are fluorine, chlorine and iodine atoms. Preferred substituted benzyl groups are 4-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 2-methoxybenzyl, 4-nitrobenzyl, 2-nitrobenzyl, 4-chlorobenzyl and 2-chlorobenzyl.

In the compounds according to the present invention the term "C_1-C_6 alkylcarbonyl" denotes a group R-C(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkylcarbonyl groups are selected from acetyl, propionyl, isobutyryl, butyryl, valeroyl and pivaloyl. The term "cycloalkylcarbonyl" denotes a group R-C(=O)- wherein R is a cyclic hydrocarbon group as defined hereinbefore. The same counts to the selected carbonyl groups.

The term "aryl" denotes an aromatic hydrocarbon group such as phenyl- (C_6H_5-), naphthyl- ($C_{10}H_7$-), anthryl- ($C_{14}H_9$-), etc. Preferred aryl groups according to the present invention are phenyl and naphthyl with phenyl being particularly preferred.

The term "benzoyl" denotes an acyl group of the formula -CO-C_6H_5 wherein the phenyl ring may have one or more substituents.

Preferred substituents of the aryl group and in particular of the phenyl group are selected from alkyl, alkoxy, halogen and *nitro. As* substituted benzoyl groups 4-methylbenzoyl, 2-methylbenzoyl, 4-methoxybenzoyl, 2-methoxybenzoyl, 4-chlorobenzoyl, 2-chlorobenzoyl, 4-nitrobenzoyl and 2-nitrobenzoyl may be mentioned.

The term "C_1-C_6 alkoxycarbonyl" refers to a group ROC(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkoxycarbonyl groups are selected from $CH_3OC(=O)$-, C_2H_5-OC(=O)-, $C_3H_7OC(=O)$- and $(CH_3)_3COC(=O)$- and alicyclic alkyloxycarbonyl.

The term "amino acid residue" denotes the residue of a naturally occurring or synthetic amino acid. Particularly preferred amino acid residues are selected from the group consisting of glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl.

The amino acid residue may be substituted by a suitable group and as substituted amino acid residues, benzoylglycyl and N-acetylglycyl may be mentioned.

The term "carbohydrate" denotes the residue of a polyhydroxy aldehyde or polyhydroxy ketone of the formula $C_nH_{2n}O_n$ or $C_n(H_2O)_n$ and correponding carbohydrate groups are, for example, described in Aspinal, The Polysaccharides, New York: Academic Press 1982, 1983. A preferred carbohydrate group in the compounds according to the present invention is a glucuronosyl group, in particular a 1β-D-glucuronosyl group.

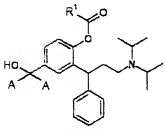
The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates, imidazolides and the like.

The term "Bn" as used herein denotes a benzyl group.

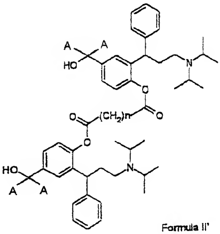
Suitable ester moieties of inorganic acids may be derived from inorganic acids such as sulfuric acid and phosphoric acid.

Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

Particularly preferred phenolic monoesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

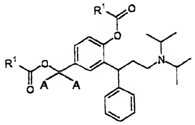
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

B) Identical diesters represented by the general formula III



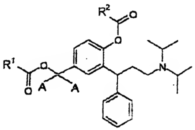
Formula III

wherein R^1 is as defined above.

Particularly preferred identical diesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diiso-propylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

C) Mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is as defined above

and

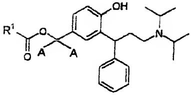
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

Particularly preferred mixed diesters are listed below:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diiso-propylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

D) Benzylic monoesters represented by the general formula V



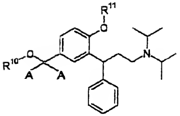
Formula V

wherein R^1 is as defined above.

Particularly preferred benzylic monoesters are listed below:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

E) Ethers and silyl ethers represented by the general formula VI



Formula VI

wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined above and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

Particularly preferred ethers and silyl ethers are listed below:

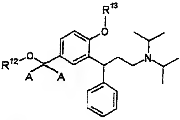
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,

(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,
(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

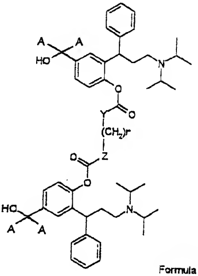
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

F) Carbonates and carbamates represented by the general formulae VII and VIII

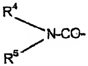


Formula VII



Formula VIII

wherein Y, Z and n are as defined above and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or

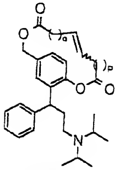


wherein R^4 and R^5 are as defined above.

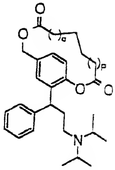
Particularly preferred carbonates and carbamates are listed below:
(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-methyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,
(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester,
(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,
(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,
(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,
(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



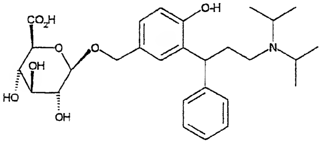
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $-(CH_2)-$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula

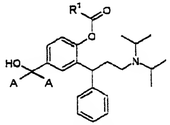


and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

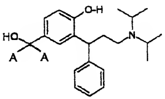
The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, the following processes are provided:

A process for the production of phenolic monoesters represented by the general formula II



Formula II

as defined above, which comprises treatment of a compound of the formula



with an equivalent of an acylating agent selected from

$$R^1\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}LG$$

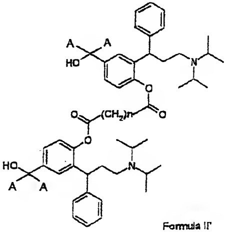
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined above, in an inert solvent in the presence of a condensating agent.

Preferably, the acylating agent is selected from

$$R^1\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}Hal \quad \text{or} \quad R^1\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}O\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}R^1,$$

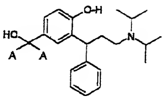
wherein Hal represents a halogen atom, preferably a chlorine atom, and R^1 is as defined above.

A process for the production of phenolic monoesters represented by the general formula II'



Formula II'

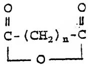
as defined above, which comprises treatment of two equivalents of a compound of the formula



with an acylating agent selected from

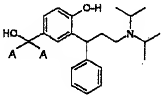
$$Hal-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-Hal$$

or



wherein Hal represents a halogen atom, preferably a chlorine atom.

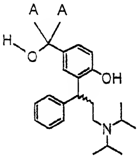
Hence, in these processes, an Intermediate B having the formula



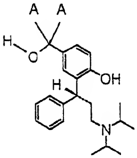
is treated with an equivalent of an acylating agent (e.g. an acyl halogenite or acyl anhydride) in an inert solvent and in the presence of a condensating agent (e.g. amine) to provide phenolic monoesters of formula II or formula II' (wherein n

is 0-12), respectively, if polyfunctional acylating agents (e.g. acid halides, preferably acid chlorides of dicarboxylic acids) are used.

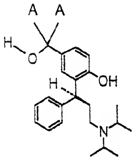
The Intermediate B as used in the processes for the production of the 3,3-diphenylpropylamines according to the present invention can be in the form of a racemic mixture or of optically active compounds in accordance with the formulae shown below:



Intermediate RS



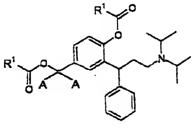
Intermediate R-(+)



Intermediate S-(-)

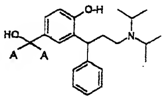
Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *"Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

The identical diesters represented by the general formula III



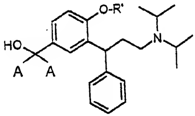
Formula III

as defined above can be prepared by a process which comprises treatment of a compound of the formula



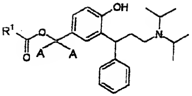
with at least two equivalents of the acylating agent R^1-C(=O)-LG as defined above.

Thus, the aforementioned di-acyl compounds are readily accessible if an at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In the above process, the following Intermediate A



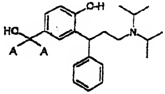
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

Benzylic monoestes represented by the general formula V



Formula V

wherein R^1 is as defined above can be prepared by a process which comprises treatment of a compound of the formula

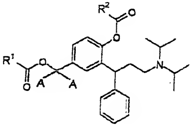


at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

Hence, this process relates to the preparation of phenols with *para* acyloxymethyl substituents (cf. formula V). These compounds can be prepared in several chemical steps from intermediates such as formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P.G.M. Wuts, "*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room tempera-

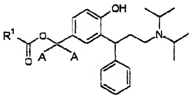
ture and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

The mixed diesters represented by the general formula IV



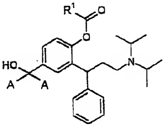
Formula IV

wherein R^1 and R^2 are as defined above can be prepared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V



Formula V

wherein R^1 is as defined above or of a phenolic monoester represented by the general formula II

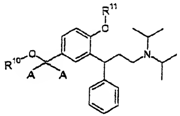


Formula II

as defined hereinbefore.

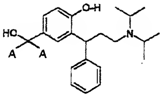
In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

Ethers represented by the general formula VI



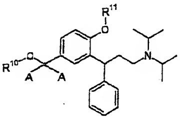
Formula VI

as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



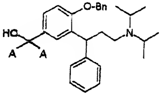
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

A further process for the preparation of ethers represented by the general formula VI

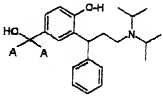


Formula VI

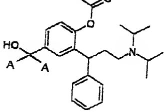
wherein R^{10} and R^{11} are as defined hereinbefore, comprises acid or base treatment of free benzylic alcohols selected from



and

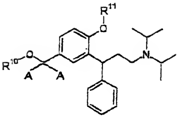


and



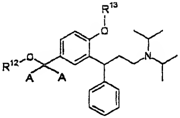
Formula II

or



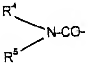
Formula VI

wherein R^{10} is hydrogen and R^{11} is as defined above or



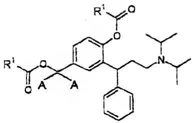
Formula VII

wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or

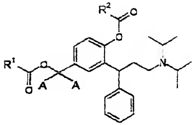


wherein R^4 and R^5 are as defined above

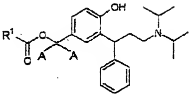
or of benzylic acylates selected from



Formula III



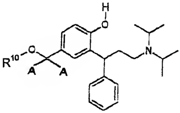
Formula IV



Formula V

wherein R^1 and R^2 are as defined hereinbefore in the presence of suitable hydroxy reagents.

Finally, ethers of formula VI can be prepared by a process which comprises treating a compound of the formula

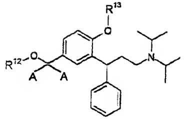


wherein R^{10} is as defined above with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

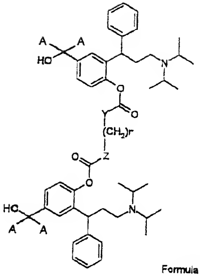
In summary, regioselective modification of the *benzylic hydroxy groups* is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J.M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P.M. Deya; J. Org. Chem. **53**: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or compounds of formulas II or VI (in which R^{10} is hydrogen) or formula VII (in which R^{12} is hydrogen) as well as benzylic acylates such as formulae III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. **30**: 1939-1942 [1989]).

Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^{11} = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis **1981**, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta **76**: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. **26**: 4307-4310 [1987]).

Carbonates and carbamates represented by the general formulae VII and VIII

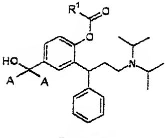


Formula VII

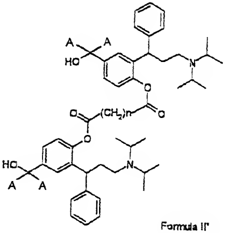


Formula VIII

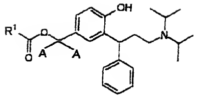
as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of



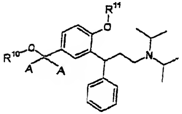
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as above, n is 0 to 12, Bn is benzyl, R^{10} or R^{11} is hydrogen with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10°C to the refluxing temperature of the solvent or reagent used to provide compounds of the general formula VII where R^{12} represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and R^{13} represents $-C(=O)-Y-R^3$, wherein Y and R^3 represent O, S, NH and alkyl or aryl, respectively. Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of formula VIII where X, Y have the meaning of O, S, or NH and n is zero to twelve.

The invention, moreover, relates to pharmaceutical compositions comprising one or more of the aforementioned 3,3-diphenylpropylamines. In other words, the compounds according to the present invention can be used as pharmaceutically active substances, especially as antimuscarinic agents.

They can be used for preparing pharmaceutical formulations containing at least one of said compounds.

The compounds according to the present invention in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of claims 1 to 15 in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as water, gelatine, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in

the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0.05 mg to about 50 g each.

The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

I. Experimental

1. General

All compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy (Bruker DPX 200). The chemical shifts reported for ^{13}C NMR spectra (50 MHz, ppm values given) refer to the solvents $CDCl_3$ (77.10 ppm), dideuterio dichloromethane (CD_2Cl_2, 53.8 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm), respectively. ^1H NMR data (200 MHz, ppm) refer to internal tetramethylsilane).

Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution.
Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%);(2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/triethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%); (7), cyclohexane/acetone/acetic acid (80/20/0.5, v/v-%).
Optical rotations were measured at 589.3 nm and room temperature on a Perkin Elmer Polarimeter Type 241.
Melting points (mp) reported are uncorrected and were determined on a Mettler FP 1 instrument.
IR spectra were taken from a Perkin-Elmer FTIR spectrometer Series 1610, resolution 4 cm^{-1}.
Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance (%) reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives.
Combined liquid chromatography-mass spectrometry (LC-MS): Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z values and relative abundance reported.

2. Synthesis of Intermediates A and B

3-Phenylacrylic acid 4-bromophenyl ester

An ice-cooled solution of 4-bromophenol (69.2 g) and cinnamoyl chloride (66.8 g) in dichloromethane (150 ml) was treated with triethylamine (40.6 g). After stirring for 18 hrs at

room temperature the mixture was washed with water (250 ml), 1 M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0 g, 99.8% yield), m.p. 113.3°C, tlc: (1) 0.83. NMR($CDCl_3$): 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

(±)-6-Bromo-4-phenylchroman-2-one

A portion of the ester (60.0 g) was dissolved in a mixture of acetic acid (60 ml) and concentrated sulphuric acid (18 ml) and refluxed for 2 hrs. After cooling, the reaction mixture was poured into ice water and the product was isolated by extraction with ethylacetate. Evaporation of the solvent and recrystallization of the residue from boiling ethanol (150 ml) yielded 26.3 g (43.8% yield) of pure, crystalline *(±)-6-bromo-4-phenylchroman-2-one*, m.p. 117.8°C, tlc: (1) 0.67. NMR ($CDCl_3$): 36.56, 40.51, 117.29, 118.87, 127.47, 127.89, 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester

A suspension consisting of (±)-6-bromo-4-phenylchroman-2-one (85.0 g), anhydrous potassium carbonate (46.7 g), sodium iodide (20.5 g) and benzyl chloride (40.6 g) in methanol (350 ml) and acetone (350 ml) was refluxed for 3 hrs. After evaporation of the solvents the residue was extracted with diethyl ether (2 x 300 ml) and the extract was washed with water (2 x 200 ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8 g (102.1% crude yield) of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* as a light yellow oil, tlc: (1) 0.77; NMR ($CDCl_3$): 39.22, 40.53, 51.63, 70.16, 113.10, 113.77, 126.46,

126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

(±)-3-(**2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid**
A solution of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionic acid methyl ester* (0,391 g, 0,92 mmol) in ethanol (5 ml) was treated at 50°C with excess aqueous sodium hydroxide solution until the milky emulsion became clear. The reaction mixture was then acidified (pH 3), evaporated and extracted with dichloromethane. The organic extract was evaporated and the remaining oil was redissolved in a minimum of boiling ethanol. The precipitation formed after 18 hrs at 4°C was filtered off and dried in vacuo to yield 0,27 g (71.4%) of *(±)-3-(2-Benzyloxy)-5-bromophenyl)-3-phenylpropionic acid*, colourless crystals, m.p. 124.9°C; tlc: (1) 0.15 (starting material methyl ester 0.75); NMR ($CDCl_3$): 39.15, 40.26, 70.25, 113.21, 113.90, 126.62, 127.27, 127.98, 128.17, 128.47, 128.54, 130.46, 130.68, 134.34, 136.45, 142.16, 154.95, 177.65. LC-MS: 412/410 (14/11%, $M^{+\cdot}$), 394/392 (15/13%), 321/319 (17/22%), 304/302 (17/21%), 259 (24%), 194 (22%), 178 (21%), 167 (65%), 152 (49%), 92 (100%). IR (KBr): 3434, 3030, 1708, 1485, 1452, 1403, 1289, 1243, 1126, 1018, 804, 735, 698, 649. Calculated for $C_{22}H_{19}BrO_3$ (mol-wgt. 411.30): C 64.25%, H 4.66%, Br 19.43%, O 11.67%; found: C 63.72%, H 4.70%, Br 19.75%, O 11.80%.

Alternatively, the crude reaction mixture from the above described synthesis of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* was evaporated, redissolved in warm ethanol, and treated with excess aqueous potassium hydroxide solution. Acidification to pH 3 (conc. hydrochloric acid) and cooling to 4°C resulted in the formation of a solid, which was filtered off after 18 hrs, washed repeatedly

with water and dried to yield *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* in 82% yield.

a) **Resolution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid**

R-(-)-3-(2-**Benzyloxy-5-bromophenyl)-3-phenylpropionic acid**
Warm solutions of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* (815.6 g, 1.85 mol) and 1S,2R-(+)-ephedrine hemihydrate (232.1 g, 1.85 mol) in 2000 ml and 700 ml, respectively, of absolute ethanol were combined and then allowed to cool to 0°C. The precipitate formed was collected, washed with cold ethanol and dried in vacuum to give 553.2 g of the ephedrinium salt of the title compound (m.p. 153°C, e.e. 65% as determined by NMR and HPLC). The salt was recrystallized twice from boiling ethanol to give *R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1S,2R-(+)-ephedrinium salt* in 75% yield, colourless crystalls, m.p. 158.6°C, e.e. 97.6% (HPLC). NMR ($CDCl_3$): 9.53, 30.90, 41.54, 42.83, 61.45, 70.15, 70.42, 113.05, 113.68, 125.89, 126.03, 127.33, 127.85, 128.19, 128.28, 128.45, 129.86, 130.70, 135.91, 136.65, 140.40, 144.09, 155.20, 178.94.

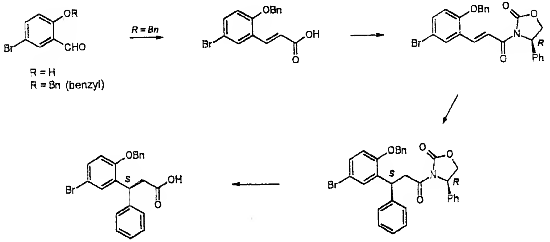
1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 ml) and dichloromethane (10 ml). The organic phase was separated, washed twice with water (2 ml), and evaporated to dryness to give *R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid* as a colourless oil which slowly solidified (0.4 g, 98% yield), m.p. 105.6°C (from ethyl acetate/n-

heptane); tlc: (7) 0.21; $[\alpha]_D^{20}$ = -21.1 (c = 1.0, ethanol), e.e. 99.9% (HPLC). NMR: identical with the racemic acid.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
The combined mother liquids from the above resolution and recrystallizations were treated under stirring and cooling (18°C) with excess conc. aqueous hydrochloric acid. The precipitate (ephedrinium hydrochloride) was filtered off, and the filtrate was evaporated to dryness. The residue was redissolved in dichloromethane (1.5 litre) and then washed with several portions of 1 M aqueous hydrochloric acid followed by water. After drying (Na_2SO_4), filtration, and evaporation 479 g of crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid were obtained as a yellow viscous oil. The pure S-(+) enantiomeric acid was converted into the 1R,2S-(-)-ephedrine salt as described above for the R-(-) acid. Two recrystallizations from boiling ethanol provided colourless crystals of *S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1R,2S-(-)-ephedrinium salt* in 83% yield, m.p. 158.7°C, e.e. 97.8% (HPLC). NMR ($CDCl_3$): 9.47, 30.85, 41.54, 42.92, 61.48, 70.13, 70.30, 113.04, 113.66, 125.89, 126.01, 127.32, 127.84, 128.18, 128.44, 129.83, 130.68, 135.94, 136.63, 140.44, 144.13, 155.19, 178.94.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid was obtained in quantitative yield from this ephedrinium salt by the method described above for the R-(-) acid, tlc: (7) 0.20, e.e. (NMR) > 99%, mp 105.5°C; $[\alpha]_D^{20}$ = +22.6 (c = 1.0, ethanol); NMR: identical with the racemic acid.

b) **Enantioselective Synthesis of R-(-)- and S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid**



2-Benzyloxy-5-bromobenzaldehyde

To a solution of 0.1 mol of 5-bromo-2-benzaldehyde in THF (150 ml) was added 0.1 mol of K_2CO_3 and 0.11 mol of benzyl bromide. The mixture was refluxed for 2 hrs and water (500 ml) was added. After addition of ethyl acetate (400 ml) and stirring the organic layer was washed with water, dried (sodium sulphate) and evaporated to dryness. The resulting slightly yellow solid of pure (tlc) 2-benzyloxy-5-bromobenzaldehyde was used as such in the next step.

3-(2-Benzyloxy-5-bromophenyl)-acrylic acid

A mixture of 2-benzyloxy-5-bromobenzaldehyde (0.10 mol), malonic acid (15.0 g), and piperidine (2.0 ml) in 150 ml of pyridine was first heated at 90°C for 90 min and subsequently refluxed for 0.5 hrs. After cooling to room temperature, the reaction was poured on a mixture of ice (1 kg) and concentrated aqueous hydrochloric acid (250 ml). The solid

material that precipitated after stirring for 2 hrs. was collected by suction and recrystallized from a minimum of boiling methanol.

3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one

Pivaloylchloride (7 g) was added dropwise at -30°C to a stirred solution of 3-(2-benzyloxy-5-bromophenyl)-acrylic acid (50.0 mmol) and triethylamine (15.0 ml) in 200 ml of tetrahydrofuran. After an additional hour the temperature was lowered to -50°C and (R)-2-phenyloxazolidin-2-one (9.0 g) and lithium chloride (2.5 g) were added in one portion. The cooling bath was then removed and stirring was continued over 18 hrs. The reaction was diluted with water and 3-[3-(2-benzyl-oxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one was isolated by extraction with ethyl acetate.

3-[3-(2-Benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one

To a precooled (-30°C) mixture of copper-(I) chloride (21.0 g) and dimethylsulfide (45 ml) in dry tetrahydrofuran (150 ml) was added dropwise an ethereal solution of phenyl-magnesiumbromide (0.3 mol). The mixture was stirred 20 min at the same temperature and then cooled to -40°C. A solution of 3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one (50.0 mmol) in dry tetrahydrofuran (150 ml) was added during 10 min. The cooling bath was removed and stirring was continued for 18 hrs. The mixture was quenched with half-saturated aqueous ammonium chloride solution and the product was isolated by extraction with ethyl acetate.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid

A solution of the above described 3-[3-(2-benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one in tetrahydrofuran (300 ml) and water (100 ml) was cooled to 0°C and then treated with 30% aqueous hydrogen peroxide (20 ml) followed by solid lithium hydroxide (4.3 g). Water was added after 2 hrs and the chiral auxiliary was removed by extraction with ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (10%) and crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was extracted with tert.-butyl-methylether.

HPLC analysis (Chiralpak AD, mobile phase hexane/2-propanol/trifluoro acetic acid [92:8:0.1, vol/vol-%); flow 1.0 ml/min, detection 285 nm) indicated an enantiomeric ratio 93:7 (retention times 14.8 min and 11.5 min, respectively). The e.e. of 86% of the S-(+) enantiomer can be improved to >98.5% by recrystallization of the diastereomeric salts using "nitromix" (Angew. Chem. Int. Ed. Engl. 1998, Vol. 37, p. 2349) or (1R,2S)-(-)-ephedrine hemihydrate as described above. The S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was isolated after acidification of aqueous solutions of the diastereomeric salts. It forms colourless crystals which gave an optical rotation of $[\alpha]_D^{22} = +21.6$ (c = 0.5, MeOH).

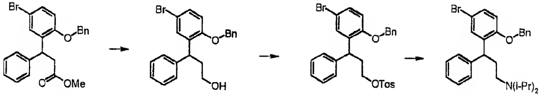
R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid

Conjugate organocuprate addition of phenylmagnesiumbromide to *3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4S)-4-phenoyloxazolidin-2-one* as described above for the S-(+)enantiomer gave crystalline R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid in an e.e. of 99.6% after two recrystalliza-

tions, $[\alpha]_D^{22}$ = -21.7 (c = 0.5, MeOH).

c) Synthesis of the R- and S- Enantiomers of Intermediate B

(i) Phenylpropanol Route



(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol
A solution of the methyl(±)-propionate (121.0 g) in 350 ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9 g) in tetrahydrofuran (350 ml). After stirring at room temperature for 18 hrs, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8 g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8°C, tlc: (1) 0.47, (±)-3-*(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol*. NMR ($CDCl_3$): 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

The same product was obtained after reduction of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* with lithium aluminium hydride in tetrahydrofuran (30 min, 25°C), 31% yield.

(±)-Toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester

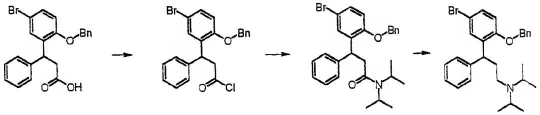
A cooled (5°C) solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0 g) in dichloromethane (300 ml) was treated with pyridine (79.4 ml) and then p-toluenesulphonyl chloride (60.6 g) in dichloromethane (200 ml). After 18 hrs. at room temperature the solvent was removed in vacuum and the residue was extracted with diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give *(±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester* as a light yellow oil after concentration under reduced pressure (140.3 g, 93.6% yield), tlc: (1) 0.66. NMR ($CDCl_3$): 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16, 155.07.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

A solution of the (±)-toluenesulphonate ((±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester, 139.3 g) in acetonitrile (230 ml) and N,N-diisopropylamine (256 g) was refluxed for 97 hrs. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500 ml) and aqueous sodium hydroxide (2 M, 240 ml). The organic phase was washed twice with water (250 ml) and then extracted with 1 M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500 ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *(±)-[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5 g, 77.9%

yield), tlc: (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70, 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

(ii) Phenylpropionamide Route



S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionyl chloride

Thionylchloride (4.5 g, 2.8 ml, 37.8 mmol) and some drops of dimethylformamide were added to a solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid (10.3 g, 25 mmol) in ethyl acetate (60 ml). The mixture was refluxed until tlc control indicated complete consumption of the starting material (2 hrs). Evaporation in vacuum gave the acid chloride as a light yellow liquid in almost quantitative yield (10.7 g). Conversion of an aliquot to the methyl ester showed a single spot in tlc (R_f 0.54, solvent system (7)).

S-(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

A solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionyl chloride (9.6 g, 22.3 mmol) in ethyl acetate (40 ml) was added dropwise to a stirred and cooled (3°C) solution of diisopropylamine (6.4 g, 49.0 mmol) in 60 ml of ethyl acetate. The reaction was stirred for 18 hrs at room temper-

ature and then washed with water, aqueous hydrochloric acid (1 M) and half saturated brine. The organic phase was dried (sodium sulphate) and evaporated to dryness. The colourless oily residue (10.7 g, 97% yield) of S-(+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide showed a single spot on tlc: (R_f 0.70 (4)). NMR ($CDCl_3$): 18.42, 20.46, 20.63, 20.98, 39.51, 41.44, 45.76, 48.63, 70.00, 112.84, 113.64, 126.10, 126.45, 127.34, 127.78, 128.20, 128.36. 129.93, 130.59, 135.18, 136.52, 143.52, 155.17, 169.61.

(±)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

The amide was prepared from diisopropylamine and the racemic acid chloride as described above for the S-(+) enantiomer. The viscous colourless oil was dissolved in ethanol and the solution stored at -30°C. From this solution colourless crystals were obtained, m.p. 101.8°C.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

To a stirred solution of (±)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide (11.8 g) in 40 ml of dry tetrahydrofuran was added 1 M lithium aluminium hydride/tetrahydrofuran (36 ml). The reaction was refluxed for 4 hrs and then quenched with the dropwise addition of water. After removal of the precipitate the solvent was evaporated and the oily residue dissolved in diluted sulphuric acid. The aqueous phase was washed several times with diethyl ether, adjusted to pH 10-12 (aqueous NaOH), and extracted with diethyl ether. The extract was dried (sodium sulphate), filtered and evaporated to dryness in vacuum to leave 8.1 g (76.7%) of the title compound as a viscous colourless oil, tlc:(4) 0.86. The NMR spectrum corresponds to the product, obtained from the

tosylate precursor (see above).

S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = +18.5 (c = 10.0, ethanol), e.e. of a representative batch 99.4%

R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = -17.3 (c = 10.0, ethanol), e.e. of a representative batch 98.3%.

The optical purities were determined by chiral HPLC using Chiralpak OD columns.

(±)-4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride

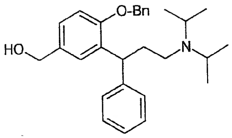
An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to -60°C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and the green reaction mixture was warmed to room temperature. After the addition of an aqueous solution of ammonium chloride (200 ml, 10%) and adjustment of the aqueous phase to

pH 0.95, a white solid was recovered by filtration to provide *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride* (14.7 g, 64.3% yield), m.p. 140°C (dec.), tlc: (2) 0.33. NMR (CD_3OD): 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol

Intermediate A (n = 1)

The (±)-hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free oily base thus obtained (28 g; tlc (2): R_f 0.46) was dissolved in dry diethyl ether (230 ml). This solution was slowly (2h) dropped under a nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8 g) in ether (140 ml). After stirring for 18 hrs, the reaction was quenched by the addition of water (4.7 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol* (26 g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4°C, tlc: (2) 0.32. NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



Intermediate A

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol

Intermediate d_2-A (n = 2)

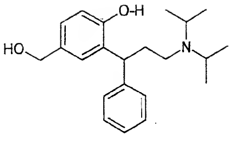
Repetition of the above described reduction of the methyl-ester of *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid* by the use of lithium aluminium deuteride gave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-[C^2H]methanol, colourless amorphous solid in 77% yield; tlc: (2) 0.33. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.96, 70.05, 111.76, 125.72, 127.34, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Intermediate B (n = 1)

A solution of Intermediate A (9.1 g) in methanol (100 ml) was hydrogenated over Raneynickel (4.5 g) under ambient conditions. After 5 hrs thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95 g, 96.5% yield) which gradually solidified, *(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol*, m.p. 50°C, tlc: (2) 0.15. NMR ($CDCl_3$): 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38.

Hydrochloride: colourless crystalls, m.p. 187-190°C (with decomposition)



Intermediate B

S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *S-(-)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 85% yield, colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol); NMR ($CDCl_3$): 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.

S-(+) hydrochloride: colourless, non-hygroscopic solid, m.p. 186.4°C (dec.); $[\alpha]_D^{22}$ = +6.6 (c = 0.5, water). NMR (DMSO-d_6): 16.58, 18.17, 31.62, 41.37, 45.90, 54.02, 63.07, 115.18, 126.05, 126.37, 128.03, 128.45, 129.04, 133.12, 143.88, 153.77.

R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 87% yield,

colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = +21.3 (c = 1.0, ethanol).

R-(-) hydrochloride: colourless, non-hygroscopic solid, m.p. 179.8°C (dec.); $[\alpha]_D^{22}$ = -7.2 (c = 0.5, water); NMR (DMSO-d_6): 16.59, 18.19, 31.64, 41.38, 45.92, 54.07, 63.08, 115.19, 126.07, 126.39, 128.04, 128.46, 129.05, 133.13, 143.89, 153.79.

S-(+)-mandelate: m.p. 139.7°C, $[\alpha]_D^{21}$ = +38.3 (c = 1.0, ethanol)

(±)**-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol**

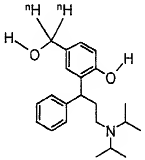
Intermediate d_2-B (n = 2)

A stirred suspension of lithium aluminium deuteride (0.1 g, 2.38 mmol) in 5 ml of dry diethyl ether was treated during 30 min at room temperature under an atmosphere of dry nitrogen with a solution of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid methyl ester (1.0 g, 2.17 mmol) in dry diethyl ether (5 ml). After an additional stirring at room temperature for 18 hrs the reaction was quenched by the dropwise addition of 0.17 ml of ^2H_2O. The resultant precipitation was filtered off, washed with small portions of ether, and the combined organic phases were evaporated to dryness in vacuum to leave

(±)-**[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol**

as slightly yellow, viscous oil which gradually crystallized, m.p. 84.1°C; tlc: (2) 0.33 (starting material 0.46), 0.725 g, 77.2% yield. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.30, 70.05, 111.76, 125.72, 125.94, 126.92, 127.34, 127.71, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

A solution of the above (±)-[4-benzyloxy-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol (0.129 g, 0.29 mmol) in a suspension of methanol (5 ml) and wet Raney-Nickel (0.1-0.2 g) was stirred at room temperature under an atmosphere of deuterium gas ($^2H_2$). After 1 hr tlc indicated complete disappearance of the starting material. The mixture was filtered, evaporated and the residue was redissolved in diethyl ether (5 ml). The solution was washed with water (2 x 5 ml), dried over sodium sulphate, filtered and evaporated to dryness to leave a pale yellow oil, 76.3 mg, in 74.6% yield, which gradually solidified to give a colourless solid of a m.p. range of 46-49°C. Tlc:(4) 0.57 (starting material 0.77). NMR ($CDCl_3$): 19.57, 19,94, 33.33, 39.56, 42.18, 48.07, 48.43, multiplett centred at 64.61, 118.47, 126.29, 126.58, 127.55, 127.94, 128.38, 132.53, 144.53, 155.37. GC-MS (P-CI, ammonia, TMS derivative): 488.43 (100%), 489.56 (70%), 490.56 (31%), 491.57 (8%).



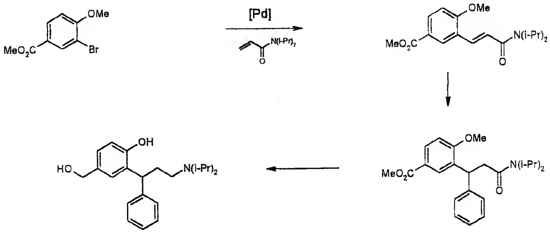
Intermediate d_2-B

n = 2, deuterium

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

Intermediate d_2-B

(iii) **Heck-Cuprate-Route to Intermediate B**



Intermediate B

N,N-Diisopropyl-acrylamide

A solution of acroyl chloride (42.2 g, 40.6 ml, 0.467 mol) in 125 ml of dichloromethane was slowly added to a cooled (0-5°C) solution of N,N-diisopropylamine in dichloromethane (500 ml). After 2 hrs the precipitated ammonium salt was filtered off and the filtrate was washed with 1M hydrochloric acid (3 x 100 ml), dried (sodium sulphate), and evaporated to dryness. N,N-diisopropyl-acrylamide was obtained as a slight yellow liquid in 48% yield and ca. 99% purity. NMR ($CDCl_3$): 20.54, 21.25, 45.66, 48.10, 125.62, 130.70, 166.17.

(E)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide

((E)-3-(2-Diisopropylcarbamoyl-vinyl)-4-methoxybenzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were

dried before use.

A stirred suspension consisting of N,N-dimethylglycine (6.0 mmol), anhydrous sodium acetate (40 mmol), methyl 3-bromo-4-methoxybenzoate (20 mmol, 4.90 g), N,N-diisopropylacrylamide (24 mmol, 3.72 g), bis-(benzonitrile)-palladium-II chloride (1.5 mol%), and 20 ml of N-methyl-2-pyrrolidinone was heated at 130°C until no starting material could be detected by tlc (starting material methyl 3-bromo-4-methoxybenzoate: R_f 0.73; N,N-diisopropylacrylamide: R_f 0.46; solvent system (1)). After cooling to room temperature 50 ml of an aqueous 2N HCl solution was added. The reaction was diluted with dichloromethane (50 ml) and the precipitated grey palladium metal was filtered off. The organic phase was washed with five portions (50 ml each) of 2N aqueous hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness. The remaining off-white solid was recrystallized from ethyl acetate/n-hexane to give 4.40 g (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide in 69% yield, m.p. 139-140°C, tlc: (1) R_f 0.40. NMR (CD_2Cl_2): 21.22, 22.10, 46.39, 48.87, 52.59, 56.61, 111.42, 123.39, 123.78, 125.54, 130.32, 132.53, 135.07. MS (EI, DI, 105°C): 319 ($M^{+\cdot}$, 22), 304 (6%), 276 (8%), 219 (100%), 187 (18%), 160 (7%).

(±)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

((±)-3-(2-Diisopropylcarbamoyl-1-phenylethyl)-4-methoxy-benzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.

A dark green solution of lithium diphenylcuprate was prepared by addition of phenyllithium solution (12 ml, 24 mmol, cyclo-

hexane/diethyl ether) to a cooled (0°C) and stirred suspension of copper-I bromide dimethylsulphide adduct (2.71 g, 13 mmol) in diethyl ether (40 ml). This solution was cooled to -78°C and then subsequently solutions were added of trimethylchlorosilane (1.5 ml, 12 mmol) in diethyl ether (5 ml) followed by the above cinnamide (3.19 g, 10.0 mmol, (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide) in 10 ml of tetrahydrofuran. The reaction was stirred for one hour at -78°C, warmed to room temperature and then quenched by the addition of 150 ml of a saturated aqueous solution of ammonium chloride. After 90 min the organic phase was washed with two portions (100 ml) of half saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated to dryness. The yellow oily residue was dissolved in a minimum of ethyl acetate and purified by column chromatography on silica gel (mobile phase (1)). Evaporation of the combined fractions of the title compound gave

(±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

as a viscous slightly yellow syrup (1.8 g, 44% yield). NMR (CD_2Cl_2): 19.45, 19.56, 19.74, 38.86, 44.87, 47.92, 50.80, 54.76, 109.41, 121.32, 125.53, 128.10, 128.43, 128.78, 132.03, 143.20, 159.95, 165.95, 168.87. MS (EI, DI, 105°C): 397 ($M^{+\cdot}$, 41%), 366 (5%), 322 (2%), 269 (3%), 255 (14%), 237 (7%), 165 (5%), 128 (12%), 91 (43%), 58 (100%).

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

A solution of (±)-N,N-diisopropyl-3-(2-methoxy-5-methoxy-carbonylphenyl)-3-phenylpropionamide (0.79 g, 2.0 mmol) in 20 ml of tetrahydrofuran was cooled to 5°C and then treated with 2.5 ml of 1M $LiAlH_4$/THF. After stirring at room tem-

perature for 18 hrs. finely powdered aluminium chloride (0.3 g) was added and stirring was continued for additional 4 hrs. The reaction was quenched at 5°C by the dropwise addition of water followed by aqueous sodium hydroxide solution. The mixture was diluted with diethyl ether (150 ml) and the organic phase was washed with half saturated brine, dried (sodium sulphate), and evaporated to dryness to give the title compound as a solid off-white foam. Tlc (2) 0.16, m.p. 48-51°C. A portion of the material was converted into the hydrochloride (ethereal hydrochloric acid), m.p. 186-189°C (dec.).

Hydrogenolytic Deoxygenation of S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A mixture of *S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (683 mg, 2.0 mmol, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol)), platinium-on-carbon catalyst (120 mg) and acetic acid (1.0 ml) was diluted with ethyl acetate (50 ml) and then hydrogenated at room temperature under a pressure of 4 bar hydrogen gas for 5 hrs. The catalyst was filtered off and the filtrate was evaporated to leave an oil. The residue was redissolved in dichloromethane (25 ml) and the solution was washed with aqueous sodium hydrogencarbonate solution. The organic phase was concentrated to dryness and the oily residue taken up in ethanol (7 ml). Addition of D-(-)-tartaric acid (300 mg) and storage of the clear solution at -25°C gave colourless crystals (310 mg) of

S-(-)-2-(3-diisopropylamino-1-phenylpropyl)-4-methylphenol D-(-) hydrogentartrate

in 33% yield, tlc: (4): 0.66 (starting material 0.31), $[\alpha]_D^{22}$ = -26.7 (c = 1.0, methanol). NMR (CD_3OD): 17.98, 18.37, 20.69, 33.68, 43.12, 56.33, 74.17, 116.31, 127.51, 129.11, 129.50, 129.70, 129.89, 130.41, 144.57, 153.67, 176.88.

A portion of the tartrate was treated with aqueous sodium hydrogencarbonate solution and the free base was isolated in quantitative yield as a colourless oil by extraction with ethyl acetate and evaporation of the extract. $[\alpha]_D^{22} = -26.3$ (c = 1.0, methanol).

Preferred intermediates in the processes for the preparation of the 3,3-diphenylpropylamines according to the present invention are:

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,

R-(-)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,

S-(+)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,

S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,

R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol and their salts.

3. Examples

a) Phenolic monoesters

aa) General procedure

Esters of Carboxylic Acids

A stirred solution of (±)-*2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenol* (Intermediate B, 1.71 g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid mono-chloride for compounds of formula II, 2.50 mmol for compounds

of formula II') in 60 ml of dichloromethane was cooled to 0°C and then triethylamine (0.502 g, 4.96 mmol for compounds of formula II, 1.05 g, 9.92 mmol for compounds of formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 min. Stirring was continued for 18 hrs at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and at low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents.
The esters of formula II or II' were obtained as colourless to light yellow solids or viscous syrups in purities between 90% and 99% (tlc, HPLC, NMR).

Esters of N-Acylamino Acids

Phenolic Monoesters

To a solution of the respective amino acid (2.0 mmol) in 0.7 ml to 5 ml of N,N-dimethylformamide and 0.5 ml of triethylamine was added at 5°C in one portion methyl chloroformate (2.0 mmol, 288 mg). After stirring for 2 hrs. at the same temperature the cooling bath was removed and a solution of Intermediate B (2.0 mmol, 682 mg) in 5 ml of dichloromethane and triethylamine (0.5 ml) was added. The reaction was allowed to stir for 2-8 hrs and then diluted with diethyl ether (70 ml). Solid precipitates were filtered off and the mixture was washed with aqueous sodium hydrogen sulphate solution (5%) and water. After drying (sodium sulphate), filtration and evaporation in vacuum the residue was purified by flash chromatography on silica gel (eluent: solvent system (4)). N-acylamino acid esters were obtained as viscous oils or waxy solids in yields between 24% and 73%.

bb) Salt formation (Example hydrochloride)

A cooled (0°C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of formula II) or 9.4 mmol (diamines of formula II') ethereal (1 M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100°C (with decomposition).

The following compounds were prepared according to the method described above and their analytical data are listed below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.47 (4), NMR ($CDCl_3$): 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%)

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.52 (4); NMR ($CDCl_3$): 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%)

(±)-n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16,

43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-Cl (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-Cl (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36

R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.38 (4), starting material: 0.26; colourless oil (yield 95%); NMR ($CDCl_3$): 19.02, 19.14, 19.96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138,76, 143.93, 147.97, 175.39.

Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +5.5 (c = 1.0, chloroform); NMR ($CDCl_3$): 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23, 34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40, 128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

(±)-2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.49 (1); NMR ($CDCl_3$): 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92, 128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; GC-MS/P-CI

(ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
((±)-2-[Diisopropylamino)-1-phenylpropyl]-4-(hydroxy-methyl)phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171.47, 173,82

(±)-Cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.66 (4), starting material Intermediate B (0.50), colourless oil, yield: 82%. NMR ($CDCl_3$): 20.42, 25.87, 30.25, 36.57, 41.89, 43.97, 47.15, 49.02, 64.63, 122.56, 125.60, 126.16, 126.81, 127.60, 127.94, 128.35, 128.77, 136.74, 138.88, 143.85, 147.92, 175.05.

(±)-Cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.67 (4), starting material Intermediate B (0.50), colourless oil, yield: 93%. NMR ($CDCl_3$): 20.27, 25.40, 25.74, 29.03, 29.16, 36.29, 41.82, 43.31, 44.08, 49.36, 64.62, 122.56, 125.68, 126.22, 126.92, 127.92, 128.38, 136.65, 139.00, 143.72, 147.86, 174.40.
(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.31 (4); colourless syrup (99% yield, purity > 95%);gradually crystallized upon refrigeration; NMR ($CDCl_3$): 20.41, 20.51, 36.65, 42.42, 43.85, 48.79, 64.70, 122.79, 125.74, 126.17, 126.83, 128.13, 128.28, 128.58, 129.48, 130.25, 133.62, 137.21, 139.10, 143.67, 148.00, 164.99.

R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
tlc R_f 0.30 (4); colourless syrup
Hydrochloride: colourless amorphous solid; $[\alpha]_D^{20}$ = +14.9 (c = 1.0, chloroform);
NMR ($CDCl_3$): 17.06, 17.53, 18.25, 18.61, 31.23, 42.19, 45.49, 54.26, 54.53, 64.09, 122.55, 126.77, 127.13, 127.58, 128.10, 128.50, 128.72, 128.78, 129.02, 130.17, 133.96, 134.27, 140.81, 142.13, 147.91, 165.40.

(±)-4-Methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.30 (4), starting material Intermediate B: 0.24; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.32, 20.50, 21.78, 36.13, 42.35, 43.98, 49.29, 64.66, 122.79, 125.81, 126.19, 126.70, 127.04, 128.30, 129.32, 129.76, 130.29, 136.94, 139.20, 143.61, 144.46, 148.04, 165.07.
LC-MS: 459 ($M^{+\cdot}$, 3.5%), 444 (17%), 223 (2.5%), 195 (2%), 119 (48%), 114 (100%).

(±)-2-Methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
viscous colourless oil, tlc: (4) 0.64 (starting material R_f 0.51), yield 84%. NMR ($CDCl_3$): 20.44, 20.53, 21.86, 22.01, 36.74, 42.36, 43.87, 48.81, 64.76, 122.93, 123.11, 125.71, 126.12, 126.88, 128.10, 128.48, 130.76, 131.26, 131.70, 132.03, 132.79, 137.28, 139.00, 141,73, 143.72, 148.04, 165.25. LC-MS: 459 ($M^{+\cdot}$, 21%), 444 (100%), 326 (1%), 223 (10%), 213 (6%), 195 (9%), 165 (14%), 115 (94%), 91 (99%).

(±)-2-Acetoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

colourless syrup, tlc: (4) 0.47 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.39, 20.57, 20.96, 36.92, 42.29, 43.88, 48.87, 64.64, 122.39, 122.64, 124.05, 125.80, 126.11, 126.75, 128.09, 128.32, 132.23, 134.66, 137.27, 139.32, 143.64, 147.63, 151.37, 162.72, 169.73. LC-MS: 503 ($M^{+\cdot}$, 7%), 488 (59%), 446 (6%), 326 (22%), 223 (9%), 213 (9%), 195 (9%), 163 (14%), 121 (100%), 114 (88%).

(±)-1-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

colourless viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.46, 20.58, 36.82, 42.46, 43.89, 48.76, 64.81, 122.98, 124.51, 125.64, 125.79, 125.98, 126.15, 126.44, 126.94, 128.12, 128.36, 128.65, 131.37, 131.82, 133.98, 134.45, 137.44, 139.08, 143.73, 148.13, 165.49. LC-MS: 495 ($M^{+\cdot}$, 8%), 480 (100%), 213 (7%), 165 (8%), 155 (95%), 127 (100%), 114 (90%).

(±)-2-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

colourless slightly yellow viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 71%. NMR ($CDCl_3$): 20.47, 20.59, 36.71, 42.59, 43.85, 48.81, 64.82, 122.89, 126.89, 127.89, 128.19, 128.41, 128.68, 129.50, 132.03, 132.55, 135.87, 137.22, 139.08, 143.83, 148.20, 165.14. LC-MS: 495 ($M^{+\cdot}$, 7%), 480 (98%), 223 (8%), 213 (6%), 195 (6%), 165 (8%), 155 (96%), 127 (100%), 114 (81%).

(±)-4-Chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.54 (4), starting material Intermediate B: 0.44; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.34, 20.50, 36.41, 42.51, 43.84, 48.93, 64.66, 122.72, 125.82, 126.88, 127.27, 128.06, 128.56, 128.96, 131.60, 133.80, 136.95, 139.30, 140.16, 143.60, 147.87, 164.10. LC-MS: 479 ($M^{+\cdot}$, 1.5%), 464 (10%), 223 (2%), 195 (2%), 165 (1.5%), 139 (25%), 114 (100%).

(±)-4-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.47 (4), starting material Intermediate B: 0.42; yield: 89%, viscous light yellow oil; NMR ($CDCl_3$): 20.31, 20.47, 36.43, 42.39, 43.90, 48.97, 55.53, 64.71, 121.79, 122.86, 125.72, 126.14, 126.79, 128.11, 128.27, 131.27, 131.77, 132.36, 132.84, 137.15, 139.01, 143.74, 148.08, 163.92, 164.71. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (20%), 223 (2%), 195 (2%), 135 (48%), 114 (100%).

(±)-2-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.40 (4), starting material Intermediate B: 0.42; yield: 98%, viscous light yellow oil; NMR ($CDCl_3$): 20.29, 20.42, 36.50, 41.92, 44.02, 49.09, 55.95, 64.72, 119.10, 120.20, 122.86, 125.64, 126.10, 126.82, 128.06, 128.30, 132.38, 134.32, 137.11, 139.01, 143.87, 148.00, 159.82, 164.40. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (18%), 223 (1%), 195 (1%), 135 (49%), 114 (100%).

(±)-4-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.44 (4), starting material Intermediate B: 0.42; yield: 78%, viscous yellow oil which slowly solidified; m.p. 123.6°C; NMR ($CDCl_3$): 20.47, 20.62, 36.52, 42.66, 43.70, 48.75, 64.69, 122.61, 123.72, 125.91, 126.33, 127.04, 128.02, 128.37, 131.32, 134.86, 136.83, 139.55, 143.56, 147.75, 150.93, 163.04. LC-MS: 490 ($M^{+\cdot}$, 1.5%), 475 (15%), 327 (0.8%), 223 (3%), 195 (3%), 150 (15%), 114 (100%).

(±)-2-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.32 (4), starting material Intermediate B: 0.42; yield: 92%, viscous yellow oil which slowly solidified; NMR ($CDCl_3$): 20.39, 20.50, 36.74, 42.14, 43.89, 48.71, 48.92, 64.59, 122.15, 123.95, 124.18, 125.89, 126.25, 127.23, 127.99, 128.39, 129.95, 132.95, 133.08, 136.72, 139.62, 143.64, 147.63, 148.15, 163.90. LC-MS: 490 ($M^{+\cdot}$, 1%), 475 (11%), 327 (2.5%), 223 (2.5%), 195 (3%), 165 (3%), 150 (7%), 114 (100%).

(±)-N-Acetylglycine 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester/(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ((±)-2-[Diisopropylamino-1-phenylpropyl]-4-(hydroxymethyl)-phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171,47, 173.82.

(±)-Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.38 (4); NMR ($CDCl_3$): 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23,

64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

(±)-Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.40 (4); NMR ($CDCl_3$): 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

(±)-Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 127.39, 127.99, 128.35, 129.31, 131.84, 136.98, 138.94, 143.80, 147.40, 169.05

(±)-Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

(±)-Identical diesters (formula III) were prepared and worked up as described above with the exception that 2.4 mmol of both triethylamine and acyl chloride (R^1-COCl) were used. The physical properties were similar to the bases and salts described above.
Diesters of N-acylaminoacids were prepared as described for phenolic monoesters with the exception that an additional molar equivalent of acylating agent (mixed acid anhydride) was used.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.65 (4). This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F. Reber, A. Lardon, T. Reichstein, *Helv. Chim. Acta* **37**: 45-58 [1954])

(±)-Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.76 (4); GC-MS/P-CI (ammonia): 426.3 (100%), 368.3 (22%); GC-MS/P-CI (methane, trimethyl-silyl derivative): 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$) - 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80, 65.21, 123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, tlc: R_f 0.82 (4); NMR ($CDCl_3$): 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; GC-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%)

(±)-n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.86 (4); NMR ($CDCl_3$): 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76,

148.41, 171.68, 173.40; GC-MS/P-CI (ammonia): 482.8 (100%), 396.4 (67%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, tlc: R_f 0.83 (4), NMR ($CDCl_3$): 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%)

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, Tlc: R_f 0.96 (4); NMR ($CDCl_3$): 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%)

(±)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

(+)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

Hydrochloride: colourless solid; tlc: (4) 0.70, $[\alpha]_D^{20}$ = +24.2 (c = 1.0, chloroform). NMR (DMSO-d_6): 16.52, 17.99, 18.06, 26.99, 31.32, 53.94, 65.98, 123.58, 127.65, 127.98, 128.62, 128.90, 129.02, 129.45, 129.71, 130.10, 133.64, 134.32, 134.55, 135.60, 142.52, 148.37, 164.53, 165.76.

c) **Mixed diesters**

Mixed diesters (formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters. Working up and physical properties corresponded to the bases and salts described above.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.76 (4); NMR ($CDCl_3$): 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.70, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.74 (4); NMR ($CDCl_3$): 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
Viscous colourless oil, tlc: R_f 0.70 (4); NMR ($CDCl_3$): identical with R-(+) enantiomer, see below.

R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
tlc: R_f 0.70 (4)
Hydrochloride: colourless non-hygroscopic solid $[\alpha]_D^{20}$ = +27.1 (c = 1.0, chloroform). NMR ($CDCl_3$): 17.14, 18.53,

21.04, 31.51, 42.25, 46.27, 54.74, 65.58, 123.18, 127.07, 127.55, 127.61, 127.99, 128.80, 130.22, 134.14, 134.81, 135.27, 141.44, 148.54, 165.19, 170.81.

(±)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18

(+)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
colourless oil
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +14.6 (c = 1.0, chloroform); NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.54, 18.92, 19.06, 20.95, 31.49, 34.07, 41.64, 46.17, 54.55, 65.49, 122.91, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

(±)-2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropyl-amino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40

(±)-2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diiso-propylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.81 (4); NMR ($CDCl_3$): 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60

d) **Benzylic monoesters**

A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 g) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2 - 24 hrs complete disappearence of the starting material (R_f = 0.45 (3)). The mixture was filtered and then evaporated under high vacuum (< 40°C) to give the carboxylic acid (R^1-CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.25 (2); NMR ($CDCl_3$): 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32

(±)-Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.26 (2); NMR ($CDCl_3$): 19.45, 20.96, 33.26, 39.63, 42.27, 48.23, 63.59, 118.00, 127.36, 128.33, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44

(±)-Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.45 (2); NMR ($CDCl_3$): 19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22

(±)-Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.54 (2); NMR ($CDCl_3$): 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05

(±)-Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.56 (4); NMR ($CDCl_3$): 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.61 (4); NMR ($CDCl_3$): 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39

(±)-Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60

e) Ethers and silyl ethers

A mixture of Intermediate B (3.4 g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^{10}-OH (50-150 ml) was stirred at room temperature until no starting material was detectable (2-24 hrs). After evaporation to dryness (< 35°C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100-200 ml, 5%, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of formula VI (R^{11} = H) as colourless to light yellow oils.

Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for examples of the structure of formula IV.

Hydrochlorides:

Molar equivalents of bases of formula VI (R^{11} = H), dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile or acetone to give colourless crystalline material.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethyl-phenol, tlc: R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl

derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%); hydrochloride: amorphous hygroscopic colourless solid; m.p. 161°C; NMR (CD_3OD): 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 129.42, 129.55, 130.43, 144.32, 155.85

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol, tlc: R_f 0.72 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 444.8 (100%), 398.4 (6%);
hydrochloride: colourless non-hygroscopic crystals, m.p. 158-161°C, NMR (CD_3OD): 15.43, 17.12, 18.82, 33.80, 56.49, 66.49, 73.62, 116.19, 127.63, 128.99, 129.13, 129.36, 129.55, 130.58, 130.75, 144.32, 155.77

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol, NMR ($CDCl_3$): 18.62, 19.44, 23.10, 33.24, 39.61, 42.26, 48.22, 71.87, 73.94, 117.78, 124.95, 127.35, 127.57, 128.32, 128.47, 133.66, 134.23, 144.48, 155.25

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethyl-phenol, NMR ($CDCl_3$): 19.44, 22.32, 33.27, 39.65, 42.29, 48.25, 69.28, 72.10, 117.90, 127.38, 128.03, 128.41, 131.10, 133.76, 134.37, 144.51, 154.65.
Hydrochloride: colourless crystals, m.p. 140.4°C, tlc (4) 0.61. LC-MS: 383 (6%, $[M-HCl]^{+\cdot}$), 368 (11%), 324 (1%), 223 (6%), 195 (3%), 165 (2%), 155 (5%), 114 (100%). NMR (DMSO-d_6): 16.57, 18.09, 18.19, 22.29, 31.58, 41.25, 45.87, 53.97, 69.26, 69.92, 115.28, 126.34, 127.08, 127.25, 127.96, 128.45, 129.07, 129.70, 132.31, 143.88, 154.22.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol, NMR ($CDCl_3$): 13.75, 19.44, 19.75, 32.24, 33.28,

39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester, NMR ($CDCl_3$): 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128,35 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester, NMR ($CDCl_3$): 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxymethylphenol, NMR ($CDCl_3$): 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28

(±)-Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$): 0.10, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98

(±)-[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxyphenyl]methanol, NMR ($CDCl_3$): 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14, 155.06

(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxy-phenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09

(±)-Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxy-phenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28

(±)-[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$): -4.92, -5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.44, 128.48, 133.37, 135.74, 144.11, 155.20

(±)-4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diiso-propylamino-1-phenylpropyl)-phenol, tlc: R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85%), 470.43 (10%), 396.3 (31%)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, NMR ($CDCl_3$): -4.77, -4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95

(±)-{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropyl-amine, tlc: R_f 0.94 (3); GC-MS/N-CI (methane): 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7

(78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

(±)-Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$): 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94

(±)-Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.87 (4); NMR ($CDCl_3$): 20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05, 137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%)

(±)-Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01; GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%)

f) Carbamates and carbonates

Mono N-substituted carbamates

A solution of 4.0 mmol of Intermediate B, benzylic ether (formula VI, R^{11} = H) or monoester of formula II in dichloromethane (20 ml) was treated at room temperature for 16 hrs with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After

washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation oily residues or colourless solids of the free bases were obtained.

N-disubstituted carbamates

N,N-dialkyl-carbamoylchloride (4.4 mmol) was dissolved in dichloromethane and dropped into a cooled (0°C) and stirred mixture consisting of Intermediate B (4.0 mmol), dichloromethane (30 ml) and triethylamine (7.0 mmol, 0.71 mg, 1 ml). Stirring was continued for 6 hrs. The mixture was then washed with 5 portions (10 ml) of aqueous sodium hydrogen carbonate, dried (sodium sulphate), filtered and evaporated to give the carbamates as colourless oils or solids.

Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65°C over 18 hrs.
Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of formulae II to IV. Alkyl chloroformates were used as acylation reagents.

Hydrochlorides:

The oils or solids were redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m.p. 64°C (with decomposition); NMR (DMSO-d_6): 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52

(±)-N,N-Dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.34, 20.66, 30.51, 36.33, 36.77, 42.00, 48.28, 50.21, 65.65, 119.83, 123.44, 125.19, 126.60, 127.38, 127.54, 129.31, 136.62, 143.33, 150.99, 155.67.

(±)-N,N-Diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.54, 20.66, 30.49, 35.61, 42.42, 48.31, 50.20, 65.56, 119.43, 123.40, 125.33, 126.66, 126.99, 127.05, 136.30, 143.27, 149.13, 154.97

(±)-N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester; NMR ($CDCl_3$): 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]acetic acid ethyl ester hydrochloride
Tlc: R_f 0.14 (4); m.p. colourless crystals (from acetone, 21% yield); NMR ($CDCl_3$): 16.76, 16.86, 18.45, 20.96, 31.37, 42.20, 46.13, 54.56, 65.50, 123.10, 126.98, 127.66, 128.72,

130.14, 134.05, 134.72, 135.22, 141.37, 148.47, 165.12, 170.71

(±)-N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester, tlc: R_f 0.36 (3); NMR ($CDCl_3$): 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74

(±)-N,N-Dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 20.59, 20.66, 30.59, 35.96, 36.40, 36.74, 36.98, 42.03, 48.26, 50.09, 67.09, 119.04, 123.23, 123.49, 125.01, 126.67, 127.72, 129.33, 133.65, 143.43, 150.99, 155.63.

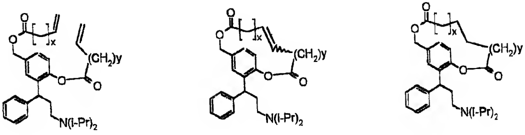
(±)-N,N-Diethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N,N-diethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 13.31, 13.64, 13.89, 20.33, 20.71, 31.57, 37.97, 41.55, 42.37, 48.46, 51.00, 67.23, 120.00, 123.39, 124.82, 126.31, 126.95, 127.33, 150.36, 157.18, 158.97.

(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-methyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (formula VII', X = Y = NH, n = 4) tlc: R_f 0.60 (6); dihydrochloride m.p. 142.5-145.6°C

(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4)

g) **Intramolecular cyclic diesters via Ring Closing Metathesis (RCM)**



Example:

(±)-Pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester (x = y = 2)

A cooled (4°C) mixture of pent-4-enoic acid, isobutyl chloroformate, and triethylamine (each 5.84 mmol) in 10 ml of dichloromethane was stirred 5 hrs under an atmosphere of dry nitrogen gas. The cooling bath was then removed and both triethylamine (1.46 mmol) and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (1.46 mmol) were added in one portion. After 18 hrs the mixture was diluted with dichloromethane (30 ml), washed several times with water and finally aqueous 5% sodium hydrogen carbonate solution. After drying (sodium sulphate), filtration and evaporation the oily residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxy-*

methyl)-phenyl ester as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$): 18.95, 20.77, 27.75, 28.87, 33.58, 36.83, 42.13, 43.72, 48.71, 65.85, 70.55, 115.47, 115.99, 122.45, 126.26, 127.08, 127.96, 128.11, 128.83, 133.73, 136.38, 136.79, 137.04, 143.77, 148.46, 171.11, 172.78.

Intramolecular cyclic diesters of 1,ω-dioic acids and Intermediate B

Example

Intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Grubbs catalyst (benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium, 16 mg, 0.002 mmol, 2 mol-%) was added to a solution of *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester* (483 mg, 0.96 mmol) in dichloromethane (150 ml) and the mixture was refluxed for 96 hrs. under an atmosphere of nitrogen gas, after which all of the starting material was consumed as indicated by tlc. The mixture was filtered through a short pad of basic alumina, and the solvent was removed in vacuum. Flash chromatography (solvent system (4)) afforded the intermediate intramolecular cyclic diester of oct-4-ene-1,8-dioic acid and 2-(3-diisopropylamino)-1-(phenylpropyl)-4-hydroxymethyl-phenol (324 mg) as a colourless syrup (tlc: (4) R_f 0.68) in 71% yield, mixture of two geometrical isomers. NMR ($CDCl_3$, major isomer): 19.24, 20.61, 23.11, 25.62, 30.55, 33.53, 35.02, 42.41, 48.29, 50.20, 65.30, 114.46, 124.33, 125.58, 127.15, 128.70, 129.29, 131.10, 132.46, 139.54, 146.76, 147.98, 173.76, 174.39.

A portion of this material (140 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature in the

presence of palladium-on carbon catalyst to afford the *intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol* in essentially quantitative yield, 139 mg, colourless oil, tlc: (4) 0.71.

NMR ($CDCl_3$): 19.36, 20.73, 24.84, 25.28, 28.90, 29.70, 30.57, 33.72, 34.37, 42.39, 48.26, 50.20, 65.26, 114.45, 124.37, 127.11, 128.67, 129.29, 131.18, 132.45, 139.52, 146.77, 147.69, 173.90, 174.15.

Poly-co-DL-Lactides of Intermediate B

All reagents were dried over P_2O_5 in vacuum (< 1 mbar) and at room temperature. The reactions were carried out at room temperature in an atmosphere of dry, oxygen-free nitrogen.

Low Molecular Weight Copolymer

A 15% solution of n-butyllithium (0.36 ml) was injected through a rubber septum into a stirred solution of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol (100 mg, Intermediate B) and DL-dilactide (1.5 g) in 15 ml of dry toluene. The polymerization was allowed to proceed for 4 days at room temperature. Distilled water (10 ml) was then added in order to terminate the polymerization. The organic phase was separated and slowly dropped into 200 ml of methanol. The precipitated colourless oil was treated with water (100 ml) and then dried in high vacuum for 48 hrs.

The copolymer was obtained in 72.7% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 2000-4000 and a weight content of Intermediate B of about 8.4% (NMR). Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) analysis showed a Mw of 1108 and a Mn of 702.

High Molecular Weight Copolymer

The high molecular weight copolymer was prepared as described above with the exception that 3.0 g of DL-dilactide was used. Precipitation by methanol gave a fluffy white solid which was carefully washed with water and then dried as desribed to give the copolymer in 81% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 4000-8000 and a weight content of Intermediate B of about 2.0%. Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) showed a Mw of 9347 and a Mn of 6981. Differential scanning calorimetry (DSC) provided a Tg of 42.5°C.

NMR Analysis

The ^1H NMR resonance signals of the poly-lactyl chain were clearly separated from the copolymeric part of Intermediate B (solvent $CDCl_3$):

CH_3 resonances of the poly-lactyl chain: 1.30-1.60 ppm

CH resonances of the poly-lactyl chain: 5.10-5.30 ppm

CH resonances of the connecting lactyl units with the two hydroxy groups of Intermediate B: 4.8-5.0 ppm and 5.5-5.7 ppm.

Polymer bound Intermediate B: 1.06-1.11 (CH_3), 2.20-2.30 ($CH_2\underline{\mathbf{CH_2}}$), 2.40-2.80 ($N\underline{\mathbf{CH_2}}$), 3.30-3.50 ($N\underline{\mathbf{CH}}$), 4.45-4.55 ($\underline{\mathbf{CH}}CH_2$), 4.70-4.80 ($\underline{\mathbf{CH_2}}$-OCO-lactyl), 6.70-7.30 (aryl $\underline{\mathbf{CH}}$).

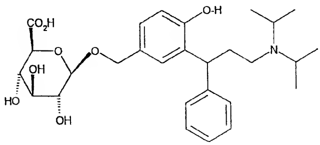
h) Inorganic ester

Example:

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester
Hydrochloride

To a stirred solution of chlorosulphonic acid (116 mg, 1.0 mmol) in 5 ml of dry diethyl ether was slowly added at 0°C a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester (445.6 mg, 1.0 mmol) in 3 ml of dry diethyl ether. The gel formed immediately during the addition was stirred at room temperature until it became a crystalline consistency (ca. 1 hr). The precipitate was washed several times with diethyl ether and then dried in vacuum to give 0.52 g (46% yield) colourless crystals, m.p. 63-65°C. NMR ($CDCl_3$): 16.85, 17.03, 18.32, 18.49, 32.01, 42.29, 46.23, 55.23, 55.50, 69.24, 122.52, 126.94, 127.15, 129.04, 129.76, 130.25, 133.89, 134.93, 136.85, 141.87, 147.80, 165.19.

i) Benzylic 1-O-β-D-glucuronide of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol
((±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol)



A solution of methyl 2,3,4-triacetyl-1-α-D-glucuronosyl-bromide (2.07 g, 4.64 mmol) in 24 ml of dry toluene was cooled to -25°C under an atmosphere of nitrogen and then treated with a solution of (±)-benzoic acid 2-(3-diisopropyl-amino-1-phenylpropyl)-4-hydroxymethylphenyl ester in 7 ml of toluene. To this mixture was added dropwise with stirring and under protection from light a solution of silver triflate in 14 ml of toluene (immediate formation of a white precipitate). The cooling bath was removed after 15 min and pyridine (0.38 ml) was added. The mixture was diluted with ethyl acetate (200 ml), filtered and the clear yellow filtrate was washed sequentially with aqueous solutions of sodium thiosulphate (5%), sodium hydrogen carbonate (5%), and sodium chloride (20%). The solution was dried with solid sodium sulphate, treated with charcoal, filtered and evaporated to dryness. The waxy residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(2,3,4-triacetyl-1β-D-glucuronosyloxymethyl)-phenyl ester*, colourless syrup, tlc (4) 0.70 (starting amine: 0.31, bromo glycoside: 0.23), yield 14%.

NMR ($CDCl_3$, mixture of diastereomers): 20.41, 20.50, 20.60, 20.65, 20.84, 36.49, 42.44, 43.65, 48.73, 52.91, 69.46, 70.43, 71.12, 72.11, 72.60, 73.99, 99.19, 122.91, 126.23, 126.38, 126.54, 127.60, 127.92, 128.06, 128.09, 128.31, 128.59, 129.38, 130.22, 133.67, 134.31, 137.41, 143.52, 148.46, 164.82, 167.26, 169.21, 169.39, 170.07.

A portion (350 mg) of the above described material was dissolved and hydrolyzed in a solvent mixture consisting of tetrahydrofuran/methanol/aqueous potassium hydroxide (excess, 12 hrs, 22°C). The mixture was evaporated, re-dissolved in 5 ml of water and the pH was adjusted to 8.3. This solution was applied to a chromatography column charged with prewashed XAD 2 resin (50 g). The column was washed with water (ca. 250 ml) and then eluted with methanol. Collection of the appropriate methanol fractions, and evaporation of the combined fractions in vacuum gave 111 mg of

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol, sodium salt,

amorphous colourless solid, m.p. ≅ 110-124°C (dec.), tlc (4) 0.12. NMR (CD_3OD, major isomer): 19.43, 19.67, 33.26, 39.63, 42.27, 48.23, 69.76, 73.55, 74.70, 75.95, 78.03, 107.64, 117.95, 125.51, 127.36, 128.33, 133.83, 134.77, 144.49, 155.36, 176.76.

II. Incubations of different compounds of the invention with human liver S 9-fraction

a) Incubation of unlabelled substrates

A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

The pooled human liver S 9-preparation was delivered by Gentest, Woburn, MA, USA.

In a routine assay, 25 µL of pooled human liver S9 (20 mg protein/mL, H961, Gentest, Woburn, MA, USA) was incubated

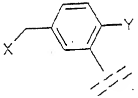
for 2 hrs at 37°C with 40 μM substrate in a 0.01 M potassium phosphate buffer in the presence of NADPH (1 mM). The reaction was quenched by the addition of concentrated perchloric acid and precipitating protein was removed by centrifugation. The supernatant was adjusted to pH 3 with concentrated potassium phosphate solution, centrifuged, and injected into the HPLC for analysis of the respective products.

The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

The incubation results expressed in (%) of theoretical turnover are presented in Fig. 1.

They ranged from 96 to 63.2%. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:
The prodrugs introduced in the assay show the following chemical structure:



chemical structure	X-/-Y	
AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and n-butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate

iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	n-butyrate
PropO-/-OProp	means	proprionate
HO-/-OProp	means	hydroxy and proprionate
HO-/-OAc	means	hydroxy and acetate
BzO-/-OBz	means	benzoate and benzoate
AcO-/-OiBut	means	acetate and isobutyrate
AcO-/-OBz	means	acetate and benzoate

b) Incubation of labelled substrates

The metabolic degradation of the unlabelled hydroxy metabolite (i.e. Intermediate B) and the deuteriated hydroxy-metabolite (Intermediate d_2B) were compared in vitro. Used were the respective enantiomers and the racemates.

The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate to produce the corresponding carboxylic acid.

The measurement was performed with an incubation time of 3 hrs at 37.0°C in a concentration of 40 μM. The formation of the carboxylic acid from the deuteriated hydroxy-metabolite showed a significantly decreased velocity of 10%.

These in-vitro experiments indicate a reduced metabolic turnover of the deuteriated compound in vitro, which may result in higher plasma levels.

c) Receptor binding study

WO 94/11337 discloses that the active metabolite has high affinity to muscarinic receptors in the guinea-pig bladder. Different compounds of the present invention were tested in

a well established standardized assay, measuring the binding of [^{3}H]-methylscopolamine to recombinant human M3 receptors. BSR-M3H cells transfected with a plasmid encoding the human muscarinic M3 receptor were used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. An aliquot of the membrane preparation was incubated with [^{3}H]-methylscopolamine in the presence or absence of different concentrations of several compounds of the invention for 60 minutes at 25°C. Nonspecific binding was estimated in the presence of 1 μM atropine. Membranes were filtered and washed three times and the filters were counted to determine the amount of [^{3}H]-methylscopolamine specifically bound. The following table shows the IC_{50} values of several compounds of the invention in the M3 receptor binding assay.

Interaction with human M3 receptors in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	8.7
(-)HO-/-OH	1300
(+)HO-/-OiBut	159
(+)HO-/-OBz	172
BzO-/-OBz	2400
AcO-/-OiBut	3600
AcO-/-OBz	5400

These data clearly showed that derivatization at the phenolic hydroxyl moiety results in an about 20 times less potent binding. If both functionalities are derivatized, the binding is even more dramatically reduced. Furthermore, it is demonstrated that the enantiomers of the active metabolite exhibit a marked difference in the binding characteristics to human M3 receptors.

The compounds were tested for their anticholinergic activity in a standard tissue assay, the guinea-pig ileum. A segment of ileum was obtained from Duncan Hartley guinea-pigs which were sacrified by cervical dislocation. The tissue was placed under 1 g tension in a 10 ml bath containing Krebs' solution (pH 7.4, 32°C) and the concentration-dependent ability of different compounds to reduce the methacholine-induced (0.6 μM) contractile response was recorded. The IC_{50} values for the different substances were calculated and examples are presented in the following table.

Anticholinergic activity in guinea-pig ileum in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	20
(-)HO-/-OH	680
(+)HO-/-OiBut	57
(+)HO-/-OBz	180
(+)BzO-/-OBz	220
(+)AcO-/-OiBut	240

These data confirm the results obtained in the receptor binding assays and demonstrate that the anticholinergic activity of the compounds decreases with increased derivatization.

d) Biological membranes

Different compounds of the invention were tested for their ability to penetrate the human skin (200 μm thick) in the "Flow through cell" at 32°C according to Tiemessen et al. (Acta Pharm. Technol. 1998; 34:99-101). Phosphate buffer (pH 6.2) was used as the acceptor medium. Samples were drawn at different time points and analysed by RP-HPLC with UV de-

tection (220 nm). Permeation profiles were plotted and mean flux rates of different substances were calculated by linear regression analysis. The data obtained for different compounds of the invention are summarized in the following table.

Penetration through human skin

Prodrug	Flux rate [$\mu g/cm^2/24hrs$]
HO-/-OH	3
HO-/-OiBut	150
iButO-/-OiBut	60
PropO-/-OProp	70

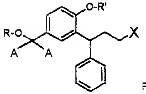
Disubstitution of the hydroxy group of HO-/-OH leads to a ≥ 20-fold increase in skin permeation in relation to the parent HO-/-OH. Suprisingly monosubstitution of the penolic hydroxy group resulted in even higher 50-fold penetration rate through human skin.

Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite, once they have entered the systemic circulation as shown by the in vitro metabolism by the human liver S9 preparation.

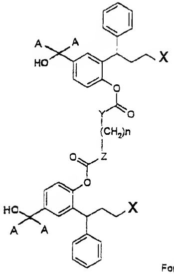
Thus, the antimuscarinic prodrugs according to this invention showed a profile that defines excellent prodrugs.

Claims

1. 3,3-Diphenylpropylamines of the general formulae I and VII':



Formula I



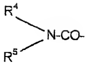
Formula VII'

wherein R and R' are independently selected from

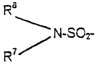
a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d) 

wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

e) 

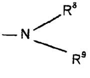
wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R' is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

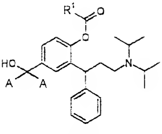
and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

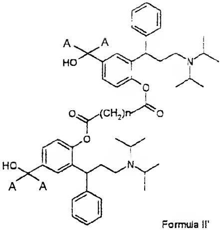
2. 3,3-Diphenylpropylamines as claimed in claim 1, wherein X is

$$-N\begin{matrix} \diagup CH(CH_3)_2 \\ \diagdown CH(CH_3)_2 \end{matrix}$$

3. 3,3-Diphenylpropylamines as claimed in claim 2 selected from phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

4. 3,3-Diphenylpropylamines as claimed in claim 3 selected from:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

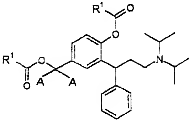
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester.

5. 3,3-Diphenylpropylamines as claimed in claim 2 selected from identical diesters represented by the general formula III



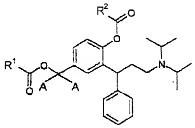
Formula III

wherein R^1 is defined as in claim 3.

6. 3,3-Diphenylpropylamines as claimed in claim 5 selected from:
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

7. 3,3-Diphenylpropylamines as claimed in claim 2 selected from mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is defined as in claim 3

and

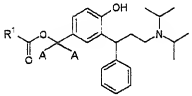
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

8. 3,3-Diphenylpropylamines as claimed in claim 7 selected from:
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

9. 3,3-Diphenylpropylamines as claimed in claim 2 selected from benzylic monoesters represented by the general formula V



Formula V

wherein R^1 is defined as in claim 3.

10. 3,3-Diphenylpropylamines as claimed in claim 9 selected from:
(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

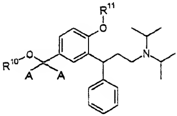
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. 3,3-Diphenylpropylamines as claimed in claim 2 selected from ethers and silyl ethers represented by the general formula VI



Formula VI

wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined in claim 1 and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

12. 3,3-Diphenylpropylamines as claimed in claim 11 selected from:

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxy-methylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-tri-methylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,

(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,

(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diiso-propylamino-1-phenylpropyl)-phenol,

(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-di-phenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropyl-amine,

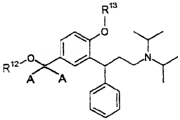
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester,

(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester,

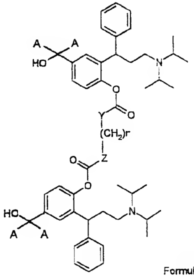
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucurono-syloxymethyl)-phenol.

13. 3,3-Diphenylpropylamines as claimed in claim 2 selected from carbonates and carbamates represented by the general formulae VII and VIII

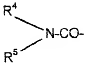


Formula VII



Formula VIII

wherein Y, Z and n are as defined in claim 1 and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



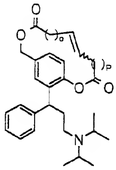
wherein R^4 and R^5 are as defined in claim 1.

14. 3,3-Diphenylpropylamines as claimed in claim 13 selected from:
(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,
(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester,
(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,
(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,
(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,
(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

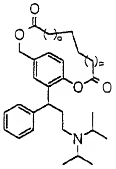
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

15. 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



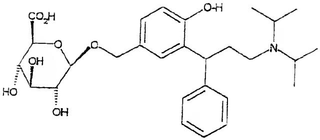
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $\left(CH_2 \right)$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenyl-propyl)-4-hydroxymethyl-phenol

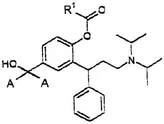
(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula



and

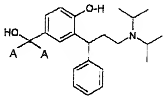
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

16. A process for the production of phenolic monoesters represented by the general formula II



Formula II

as defined in claim 3, which comprises treatment of a compound of the formula

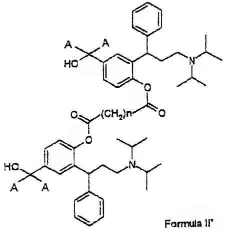


with an equivalent of an acylating agent selected from

$$R^1-\overset{\overset{\displaystyle O}{\|}}{C}-LG$$

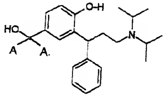
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined in claim 3, in an inert solvent in the presence of a condensating agent.

17. A process for the production of phenolic monoesters represented by the general formula II'



Formula II'

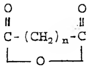
as defined in claim 3, which comprises treatment of two equivalents of a compound of the formula



with an acylating agent selected from

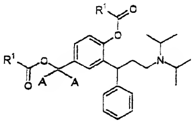
$$\mathrm{Hal{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}(CH_2)_n{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}Hal}$$

or



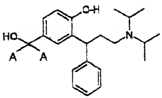
wherein Hal represents a halogen atom.

18. A process for the production of identical diesters represented by the general formula III



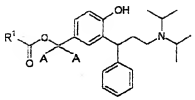
Formula III

as defined in claim 5, which comprises treatment of a compound of the formula



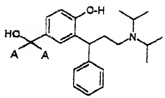
with at least two equivalents of the acylating agent as defined in claim 16.

19. A process for the preparation of benzylic monoesters represented by the general formula V



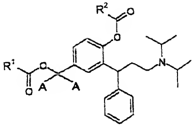
Formula V

as defined in claim 9, which comprises treatment of a compound of the formula



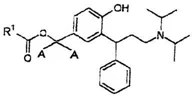
at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

20. A process for the preparation of mixed diesters represented by the general formula IV



Formula IV

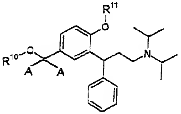
as defined in claim 7, which comprises acylation of a benzylic monoester represented by the general formula V



Formula V

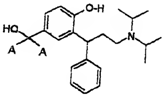
as defined in claim 9 or of a phenolic monoester represented by the formula II as defined in claim 3.

21. A process for the production of ethers represented by the general formula VI



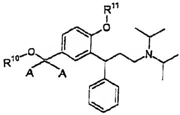
Formula VI

as defined in claim 11 wherein R^{11} is hydrogen which comprises reacting a compound of the formula



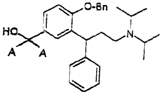
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

22. A process for the preparation of ethers represented by the general formula VI

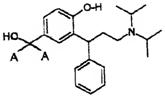


Formula VI

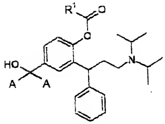
wherein R^{10} and R^{11} are as defined in claim 11, which comprises acid or base treatment of free benzylic alcohols selected from



and

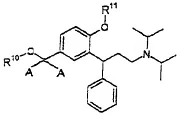


and



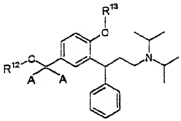
Formula II

or



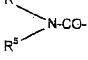
Formula VI

wherein R^{10} is hydrogen or

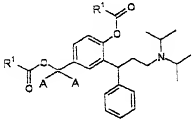


Formula VII

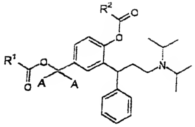
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



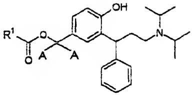
wherein R^4 and R^5 are as defined in claim 1 or of benzylic acylates selected from



Formula III



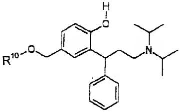
Formula IV



Formula V

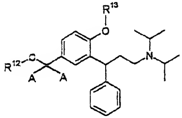
wherein R^1 and R^2 are as defined in claim 7 in the presence of suitable hydroxy reagents.

23. A process for the preparation of ethers of formula VI as defined in claim 11, which comprises treating a compound of the formula

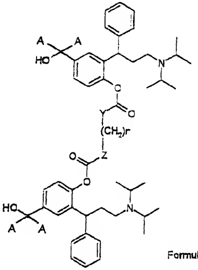


with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

24. A process for the preparation of carbonates and carbamates represented by the general formulae VII and VIII

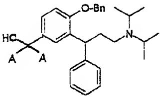


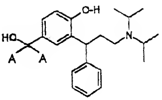
Formula VII

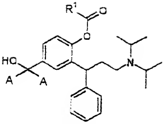


Formula VIII

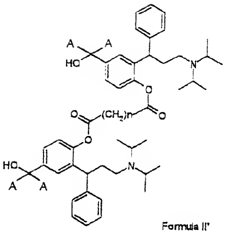
as defined in claim 13, which comprises reacting a compound selected from the group consisting of



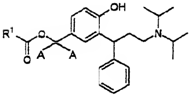




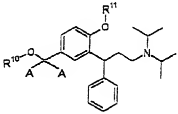
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as in claim 3, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is as defined in claim 11 with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

25. 3,3-Diphenylpropylamines as claimed in claims 1 to 15 for use as pharmaceutically active substances, especially as antimuscarinic agents.

26. A pharmaceutical composition comprising a 3,3-diphenyl-propylamine as claimed in claim 1 to 15 and a compatible pharmaceutical carrier.

27. Use of a 3,3-diphenylpropylamine as claimed in claims 1 to 15 for preparing an antimuscarinic drug.

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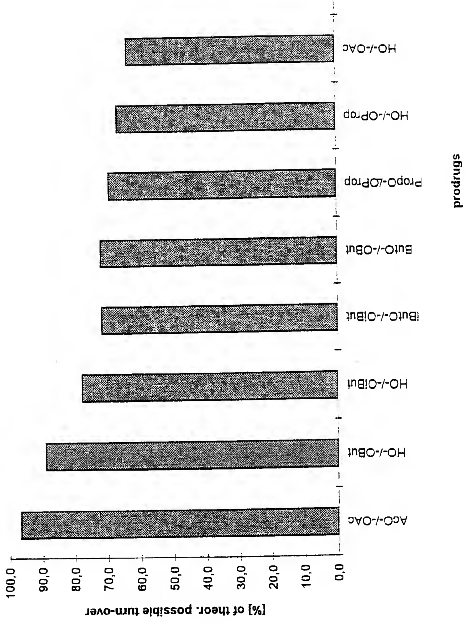
FIG. 1

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h



INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 99/03212

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C1/00 C07C217/62 C07C217/48 C07C219/28 C07C219/22 C07D207/06 C07D295/06 C07C271/08 C07F7/18 C07C307/02 A61K31/135 A61K31/325 A61K31/40 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 89 06644 A (KABIVITRUM AB) 27 July 1989 (1989-07-27) abstract	1-3, 25-27
A	LISBETH NILVEBRANT ET AL.: "Tolterodine - a new bladder-selective antimuscarinic agent" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 327, 1997, pages 195-207, XP002079629 cited in the application the whole document	1,25-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 July 1999	26/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rufet, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
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